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AUREOMYCIN IN THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN*

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AUREOMYCIN is an antibiotic derived from a strain of *Streptomyces aureofaciens*. The drug has been found to have a wide antibacterial spectrum against gram-positive and gram-negative organisms. In addition, it has been found to be effective against rickettsia as well as certain viruses, chiefly of the lymphogranuloma-venereum-psittacosis group.[1] In man, therapeutic doses up to 60 mg. per kilogram of body weight per day given orally have not been associated with toxic manifestations except for occasional nausea, vomiting and diarrhea. These symptoms have been transient and do not contraindicate or prevent continuation of therapy.

Aureomycin is absorbed readily after oral administration, and the maximum rate of excretion in the urine occurs between four and eight hours after the dose.[2] Thus, an interval between doses of four to six hours can be considered optimum. The oral route is the preferable mode of administration. Intramuscular injection is accompanied by local pain and sometimes induration and tenderness. Aureomycin may be given intravenously, but this method of administration was not employed in our series.

A study to evaluate the efficacy of aureomycin¶ in the treatment of pneumonia in infants and children was instituted in January, 1949. This investigation was prompted by the observation that the drug is effective against the bacteria most frequently responsible for pneumonia and by published reports of its value in the treatment of atypical viral pneumonia.[3, 4] It has been found that strains of pneumococcus, streptococcus and *Haemophilus influenzae* are almost completely inhibited by aureomycin in concentrations of 1 microgm. per cubic centimeter or less.[5] Such a blood concentration is readily obtained with therapeutic doses of the drug. Recently, Schoenbach and Bryer[3] and Finland and his co-workers[4] reported small series of cases of primary atypical pneumonia that responded well to aureomycin. This constitutes the first indication of any effective antibiotic agent in viral pneumonia, all previous therapy having been found to be ineffective.

Thus, aureomycin, because of its versatility, seems to be an extremely valuable agent in the treatment of pneumonia. A drug that is effective against both viruses and bacteria embraces a considerably larger antimicrobial range than either sulfadiazine or penicillin (or both combined) and should be effective against the vast majority of pneumonias encountered in the pediatric age group.

MATERIALS AND METHODS

In view of these considerations it was believed that aureomycin warranted a clinical trial. To this end, a special pneumonia ward was set up at the Children's Hospital. So far as possible consecutive patients who had clinical and roentgenologic evidence of pneumonia were treated with aureomycin on admission to the hospital. These patients either had not received previous therapy or had not been benefited by chemotherapy or antibiotics.

A uniform plan of study was employed in all cases, including nasopharyngeal and blood cultures, blood counts, x-ray examination of the chest, agglutinins for streptococcus MG and cold hemagglutinins at periodic intervals during the course of therapy. Nearly all the patients were seen in the follow-up clinic approximately three weeks after the onset of illness. At this time each patient was re-examined, and blood was drawn for follow-up streptococcus MG and cold hemagglutinin titers.

Examination of the flora of the nasopharynx has been reported to be a fairly reliable procedure in determining the causative agent of pneumonia in children.[6] It should be remembered, however,

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that isolation of an organism from the nasopharynx is, at best, only partial evidence that it is the organism responsible for the disease in the lower respiratory tract. In the opinion of Alexander et al.[7] the presence of substantial numbers of pneumococci in the nasopharynx of a child with pneumonia is a reliable index that the patient has pneumococcal pneumonia. The presence of a beta-hemolytic streptococcus or *H. influenzae* as the sole or predominant organism is only probable evidence that it is the pathogen in the lower respiratory tract. However, the isolation of hemolytic *Staphylococcus aureus* has little or no significance in determining the etiologic agent in pneumonia since it is found so frequently in the nasopharynx of normal children. A positive blood culture, of course, is presumptive evidence of the responsible organism of an associated pneumonia.

Thirty-nine patients fulfilling the established diagnostic requirements of pneumonia were studied. Their ages ranged from three months to eleven years and were distributed as follows: 3 patients were less than six months of age, 3 between six and twelve months, 10 from one to two years, 12 between two and five years, and 11 from six to twelve years.

Of the 39 cases in this series, 30 were classified as bacterial and 9 as viral in origin (Table 1). A pneumococcus was isolated in 16 of the 30 cases of bacterial pneumonia and a beta-hemolytic streptococcus in 2. *Staph. aureus* was cultured from the blood of an infant with a severe bilateral bronchopneumonia. The organisms cultured from the nasopharynx of the 11 unclassified patients represented the normal nasopharyngeal flora, including *Staph. aureus*, *Staph. albus*, *Streptococcus viridans* and *Neisseria catarrhalis*. The mere presence of these organisms in the upper respiratory passage was not considered sufficient to indict them as the causative agents of the pneumonia. However, the clinical manifestations together with the x-ray findings and leukocytosis were compatible with a diagnosis of bacterial pneumonia in this unclassified group.

TABLE 1. *Classification of 39 Cases of Pneumonia.*

TYPE OF PNEUMONIA	NO. OF CASES
Bacterial	30
Pneumococcal	16
Streptococcal	2
Staphylococcal	1
Unclassified	11
Primary atypical	9

In evaluating the efficacy of a new drug the severity of the illness should be taken into consideration. It was considered marked in 15 of 39 cases (38.4 per cent), moderate in 11 (28.2 per cent) and mild in 13 (33.4 per cent). Eight of the patients required oxygen. The children with bacterial pneumonia were in general more severely ill on admission than those with the viral cases.

The temperature of the patients in this series at the time of initiation of therapy ranged from 100.2 to 106°F. In 25 cases it was above 103°F. Patients in the bacterial group generally ran higher temperatures, 22 (73 per cent) having temperatures above 103°F. at the time of admission.

White-cell counts are usually elevated in pneumonias of bacterial origin and normal or depressed in the viral types. In our cases all but 1 patient with bacterial pneumonias had white-cell counts above 10,000 on admission, and 6 of the 9 with viral pneumonias had counts below 10,000.

RESULTS

The therapeutic effect of aureomycin on the pneumonias of bacterial origin was quite favorable. The over-all results (based principally on the rapidity of return to normal of clinical, roentgenologic and laboratory findings) were considered good in 24 cases, fair in 5, and poor in only 1. The results were particularly gratifying in the pneumococcal group, 14 of 16 patients showing a good response (Table 2). It is interesting that the unclassified bacterial pneumonias demonstrated a less dramatic response than the cases on which a specific organism was indicted.

TABLE 2. *Results in 39 Cases of Pneumonia Treated with Aureomycin.*

TYPE OF PNEUMONIA	RESULT		
	GOOD	FAIR	NONE
Bacterial			
Pneumococcal	14	2	—
Streptococcal	1	1	—
Staphylococcal	1	—	—
Unclassified	8	2	1
Primary atypical	7	1	1
Totals	31	6	2

In 15 (50 per cent of the 30 cases of bacterial pneumonia) the temperature returned to normal eighteen hours after initiation of aureomycin therapy. Four patients became afebrile in eighteen to thirty-six hours, and 9 maintained an elevated temperature from thirty-six to seventy-two hours. Two other patients had low-grade fevers beyond seventy-two hours, 1 for ninety-six and the other for one hundred and twenty hours. It is interesting that 9 of the 11 patients who maintained a temperature elevation beyond thirty-six hours had received aureomycin intramuscularly. In 2, a change from the intramuscular to the oral mode of administration produced a prompt defervescence within twelve to twenty-four hours.

Two infants with pneumococcal pneumonia had an associated pertussis and ran a protracted low-grade fever in spite of apparent early improvement of the pneumonia.

An evaluation of the effect of aureomycin on the pathogens of the nasopharynx was attempted. Cultures were obtained on the first, third and fifth hospital days on each patient. Of the 16 cases of pneumonia in which a pneumococcus was the predominant organism initially, 7 failed to grow out this pathogen on the second or subsequent cultures. In 4 others, pneumococci were not demonstrable on the third culture. However, in 5 cases the organism was still present in the nasopharynx after five days of aureomycin therapy. There was no apparent correlation between the interval required for the elimination of the pathogen from the nasopharyngeal cultures and the over-all clinical improvement.

Serial white-cell counts were analyzed in the patients with bacterial pneumonia treated with aureomycin. In 71 per cent of the cases of pneumococcal pneumonia the white-cell count returned to normal (5000 to 10,000) within five days of the initiation of therapy. Six of 10 patients (60 per cent) with unclassified bacterial pneumonia showed an equally prompt drop to normal after aureomycin was started. In general the decline in the white-cell count was more rapid in children who were given the drug by mouth than in those who received it intramuscularly.

Each of the patients had an x-ray examination of the chest on the day of admission. Follow-up films were taken on all but 1 child, and the majority were examined roentgenologically three or more times. A strict evaluation of the effect of aureomycin on the lesion radiologically was not possible because of the slight discrepancy in the intervals between films among the patients in the series. However, for purposes of classification, the patients were arbitrarily divided into those who showed appreciable resolution by x-ray study in seven days or less and those in whom there was little or no change in that time. There was evidence of considerable resolution of the inflammatory process within seven days in 23 of 30 patients with bacterial pneumonia. A rather striking difference was noted in the roentgenologic results in the patients with bacterial pneumonia treated orally and in those treated intramuscularly. Sixteen of the 17 cases of pneumonias treated orally resolved appreciably within seven days, whereas only 7 of 13 cases treated intramuscularly had shown resolution by x-ray examination in that time.

Treatment of Bacterial Pneumonias

The pertinent data of the 30 cases in the bacterial group are summarized in Table 3. The following 4 cases serve to illustrate the course of the various types of bacterial pneumonia treated with aureomycin.

S. L., a 7-year-old Negro, contracted a respiratory infection about 1 week before admission. For 2 days before entry he complained of pain in the left side of the chest that was aggravated by breathing. Associated symptoms included cough, headache, malaise and fever.

Physical examination revealed an acutely ill child with rapid, grunting respirations. The temperature was 103°F. The pharynx and tonsils were reddened, and there were dullness and diminished breath sounds over the left lower portion of the chest posteriorly. The white-cell count was 27,700, with 84 per cent neutrophils. Pneumococci and beta-hemolytic streptococci were cultured from the nasopharynx, and a blood culture was sterile. X-ray examination of the chest revealed an area of density in the medial two thirds of the lower left portion of the chest. The clinical course and other pertinent data are shown in Figure 1.

Shortly after admission aureomycin therapy was initiated in a dose of 250 mg. orally every 4 hours. The temperature dropped rapidly to normal eighteen hours after therapy was started, and concomitantly the patient showed a striking clinical response. Subsequent nasopharyngeal cultures failed to grow out any pneumococci. Therapy was discontinued on the sixth day after an uneventful recovery.

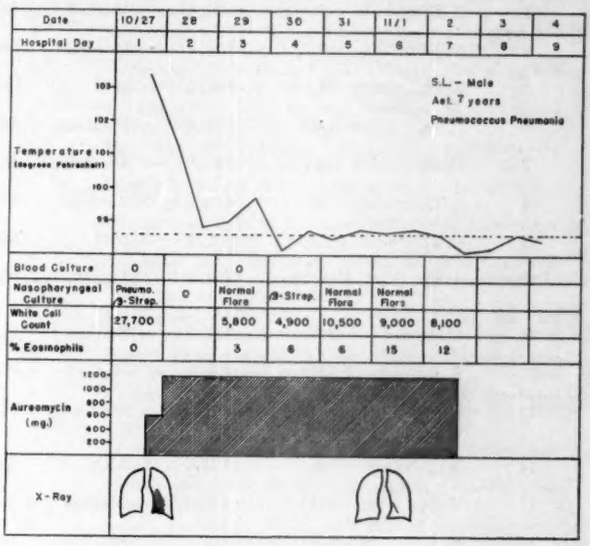

FIGURE 1. *Clinical Course and Laboratory and X-Ray Findings in S. L.*

T. D., a 5-year-old boy, was admitted to the hospital with a respiratory infection accompanied by cough of 3 days' duration. On the day before entry he became worse, with rapid respirations, a more severe nonproductive cough, pain in the left side of the chest, listlessness and anorexia.

Physical examination revealed a moderately ill, dyspneic child with a temperature of 102°F. There was dullness to percussion, and the breath sounds were diminished over the left side of the chest posteriorly.

The white-cell count was 18,500, with 75 per cent neutrophils. A blood culture was sterile. Beta-hemolytic streptococci were cultured from the nasopharynx. X-ray study of the chest revealed an area of opacity involving most of the left lower lobe and considerable infiltration throughout the right side of the chest. The course and other pertinent data are shown in Figure 2.

Aureomycin therapy was instituted shortly after admission in a dosage of 250 mg. orally every 4 hours. Within 16 hours of admission the patient was afebrile and appeared much improved. The abnormal chest signs cleared gradually, and on the 6th hospital day there was x-ray evidence of complete resolution. The drug was discontinued after 5 days, and on the 6th hospital day the child was discharged after an uneventful convalescence.

V. F., a 10-week-old Negro infant, was well until 3 days before admission, when she began to cough and had a high fever and difficulty in breathing. These symptoms increased in severity until the time of hospitalization.

Physical examination disclosed an acutely ill, dyspneic infant with a temperature of 104.8°F., a pulse of 200 and respirations of 120 per minute. There were coarse and crepitant rales at both bases. The white-cell count was 26,000, with 49 per cent neutrophils and a predominance of immature forms. Hemolytic *Staph. aureus* was cultured from the blood, and nonhemolytic *Staph. aureus* and pneumococcus were isolated from the nasopharynx. X-ray study of the chest revealed a disseminated bronchopneumonia. The course and other data are shown in Figure 3.

The patient was placed in an oxygen tent, and aureomycin was administered intramuscularly in a dosage of 10 mg. every 8 hours. The infant improved rapidly, and in 12 hours was afebrile and out of oxygen. Except for slight rises in temperature on the 2nd and 4th hospital days, recovery was uneventful. Subsequent blood cultures were negative, and aureomycin was discontinued after 8 days.

The patient in the bacterial group who was considered not to have benefited by aureo-

TABLE 3. *Summary of 30 Cases of Bacterial Pneumonia Treated with Aureomycin.*

Case No.	Patient	Age	Temperature	Severity	Location	Nasopharyngeal Culture
		yr.	*°F.*			
1	S. L.	7	103.0	Moderate	Left lower lobe	Pneumococcus; beta-hemolytic streptococcus.
2	S. M.	1 10/12	104.0	Marked	Right (broncho-pneumonia)	Pneumococcus; *N. catarrhalis.*
3	H. C.	7	103.4	Marked	Right upper lobe	Pneumococcus; gamma streptococcus; staphylococcus (nonhemolytic).
4	N. H.	7	104.4	Moderate	Left lower lobe	Pneumococcus; *N. catarrhalis.*
5	W. S.	7	104.4	Mild	Left upper lobe	Pneumococcus; *N. catarrhalis*; *H. influenzae.*
6	G. M.	8/12	104.0	Moderate	Right and left (bronchopneumonia)	Pneumococcus; *Staph. aureus* (hemolytic); *H. influenzae.*
7	D. G.	4	105.0	Moderate	Right and left (bronchopneumonia)	Pneumococcus; *Staph. aureus* (hemolytic).
8	J. T.	3	104.0	Moderate	Right lower lobe	Pneumococcus; *Staph. aureus* (hemolytic).
9	B. T.	1 4/12	106.0	Mild	Right lower lobe	Pneumococcus; *N. catarrhalis.*
10	A. C.	1 10/12	104.8	Moderate	Right upper lobe	Pneumococcus; *N. catarrhalis*; *Staph. aureus* (nonhemolytic).
11	M. P.	9/12	105.0	Marked	Right and left (bronchopneumonia)	Pneumococcus; *Staph. aureus* (hemolytic).
12	R. C.	2 4/12	103.0	Marked	Right and left (bronchopneumonia)	Pneumococcus
13	P. F.	1 4/12	105.0	Moderate	Right and left (bronchopneumonia)	Pneumococcus; *Staph. aureus* (hemolytic).
14	W. S.	6	104.0	Mild	Left lower lobe	Pneumococcus
15	V. B.	8/12	101.0	Marked	Right and left (bronchopneumonia)	Pneumococcus; *Haemophilus pertussis*; *Escherichia coli*; *Staph. aureus* (nonhemolytic).
16	E. J.	3/12	102.6	Marked	Right (broncho-pneumonia)	Pneumococcus; *H. pertussis*; *Staph. aureus* (hemolytic).
17	A. C.	6	103.0	Marked	Right lower lobe	Beta-hemolytic streptococcus; *N. catarrhalis.*
18	T. D.	5	102.0	Mild	Left lower lobe	Beta-hemolytic streptococcus
19	V. F.	3/12	104.8	Marked	Right and left (bronchopneumonia)	Pneumococcus; *Staph. aureus* (nonhemolytic).
20	V. E.	9/12	101.0	Marked	Right and left (bronchopneumonia)	*Esch. coli* (hemolytic); gamma streptococcus.
21	J. B.	10	105.2	Marked	Right and left (bronchopneumonia)	*Staph. albus* (hemolytic); gamma streptococcus.
22	G. W.	2	103.4	Moderate	Right and left (bronchopneumonia)	*N. catarrhalis*; *Staph. aureus* (nonhemolytic).
23	D. G.	1 7/12	104.8	Moderate	Right and left (bronchopneumonia)	*Staph. aureus* (hemolytic); *N. catarrhalis.*
24	B. L.	2	102.4	Mild	Right lower lobe	*Staph. aureus* (hemolytic); pneumococci (few).
25	H. B.	5	104.6	Mild	Right and left (bronchopneumonia)	*Staph. aureus* (hemolytic)
26	R. K.	6	103.6	Marked	Right and left (bronchopneumonia)	*Staph. albus* (hemolytic)
27	W. D.	5/12	103.0	Marked	Right and left (bronchopneumonia)	*N. catarrhalis*; *H. influenzae*; *Staph. albus* (hemolytic).
28	W. T.	2	104.4	Mild	Right and left (bronchopneumonia)	*Staph. aureus* (nonhemolytic)
29	H. M.	1 5/12	100.2	Marked	Right and left (bronchopneumonia)	*N. catarrhalis*; *Staph. albus* (nonhemolytic).
30	D. S.	6	100.4	Mild	Right (broncho-pneumonia)	Gamma streptococcus

*Intramuscular injection.
†Oral administration.

mycin was a six-year-old boy who was admitted to the hospital with a severe bronchopneumonia associated with measles that had previously not responded to penicillin and failed to improve after forty-eight hours of oral aureomycin. Penicillin and aureomycin were then given in combination, and the patient slowly improved, the temperature gradually returning to normal within three and a half days. An associated hematuria, albuminuria and pyuria were noted on several urine specimens during the hospital stay. Thus, the evaluation of aureomycin in this case was somewhat complicated. However, it is our impression that the drug exerted little or no salutary effect on the course of the illness.

TABLE 3 (*Continued*).

Case No.	Maximum White-Cell Count	Previous Therapy	Aureomycin Therapy			Results
			Day Initiated	Dosage	Total Duration	
				mg./kg./24 hr.	*days*	
1	27,000	None	4	41.0	6	Patient afebrile in 18 hr.; x-ray evidence that chest had cleared in 6 days; recovery uneventful.
2	40,300	None	5	46.0	6	Patient afebrile in 12 hr.; x-ray evidence that chest had cleared in 4 days; recovery uneventful.
3	11,000	None	3	60.0	5	Patient afebrile in 12 hr.; x-ray evidence that chest had cleared in 5 days; recovery uneventful.
4	25,000	None	5	62.5	4	Patient afebrile in 48 hr.; x-ray evidence that chest had cleared in 7 days; recovery uneventful.
5	21,400	None	5	55.8	5	Patient afebrile in 36 hr.; x-ray evidence that chest had cleared in 7 days; recovery uneventful.
6	28,000	None	3	13.0* 99.0†	4 5	Patient afebrile in 72 hr.; x-ray evidence that chest had cleared in 8 days; recovery uneventful.
7	16,400	None	7	60.0	5	Patient afebrile in 12 hr.; x-ray evidence that chest had cleared in 7 days; recovery uneventful.
8	14,900	None	4	55.0	6	Patient afebrile in 12 hr.; x-ray evidence that chest had cleared in 6 days; recovery uneventful.
9	16,900	None	4	84.0	4	Patient afebrile in 12 hr.; x-ray evidence that chest had cleared in 7 days; recovery uneventful.
10	18,000	None	5	7.5* 75.0†	3 2	Persisting low temperature for 72 hr.; x-ray evidence that chest had cleared in 11 days; patient afebrile 12 hr. after oral therapy.
11	15,500	None	6	83.0	3	Patient afebrile in 18 hr.; x-ray evidence that chest had cleared in 7 days; recovery uneventful.
12	18,600	None	4	15.3* 82.3†	1 4	Patient afebrile in 12 hr.; x-ray evidence that chest had cleared in 6 days; recovery uneventful.
13	12,200	None	4	7.5	5	Patient afebrile in 12 hr.; x-ray evidence that chest had cleared in 5 days; respiratory infection on 5th day, with no relapse.
14	16,600	None	3	50.0	5	Patient afebrile in 30 hr.; x-ray evidence that chest had cleared in 4 days; recovery uneventful.
15	13,200	None	3	10.0* 96.0†	2 4	Patient afebrile in 50 hr. and improved rapidly after oral therapy; chest failed to clear by 6 days.
16	12,500	None	3	10.0*	5	Patient afebrile in 60 hr.; slow clinical recovery; x-ray evidence of clearing in 7 days.
17	16,000	None	3	4.0* 56.0†	3 3	Persistent low fever for 6 days; good clinical response; x-ray evidence that chest had cleared in 4 days.
18	18,500	None	4	88.0	5	Patient afebrile in 18 hr.; x-ray evidence that chest had cleared in 5 days; recovery uneventful.
19	26,000	None	4	7.0*	8	Blood culture showed *Staph. aureus* (hemolytic); patient afebrile in 12 hr.; x-ray evidence of clearing in 5 days; recovery uneventful.
20	13,000	Penicillin; sulfadiazine.	7	6.0*	10	Patient afebrile in 12 hr.; x-ray evidence that chest had cleared in 9 days; recovery uneventful.
21	23,500	None	2	52.0	4	Patient afebrile in 6 hr.; x-ray evidence that chest had cleared in 5 days; recovery uneventful.
22	14,600	None	5	5.4*	7	Persistent low fever for 96 hr.; x-ray evidence that chest had cleared in 9 days; gradual clinical recovery.
23	21,200	None	8	3.0*	5	Patient afebrile in 12 hr.; x-ray evidence that chest had cleared in 7 days; recovery uneventful.
24	10,500	None	4	4.5*	6	Patient afebrile in 36 hr.; x-ray evidence that chest had cleared in 9 days; recovery uneventful.
25	25,000	None	2	75.0		Patient afebrile in 18 hr.; x-ray evidence that chest had cleared in 7 days; recovery uneventful.
26	27,000	Penicillin	7	47.0	10	Measles with pneumonia; no clinical response in 48 hr.: penicillin added, with gradual improvement.
27	10,000	None	5	8.1*	4	Patient afebrile in 60 hr.; x-ray evidence that chest had cleared in 4 days; recovery uneventful.
28	11,800	Sulfadiazine; penicillin.	8	60.0	3	Patient afebrile in 6 hr.; x-ray evidence that chest had cleared in 3 days; recovery uneventful.
29	12,300	Sulfadiazine	2	5.3*	5	Patient afebrile in 48 hr.; x-ray evidence that chest had cleared in 6 days; recovery uneventful.
30	9,000	Sulfadiazine	2	75.0	6	Patient afebrile in 36 hr.; x-ray evidence that chest had cleared in 3 days; recovery uneventful.

Treatment of Viral Pneumonia

The diagnosis of primary atypical pneumonia is a difficult one, and the clinical picture, especially in infants and children, is often confusing. The disease varies widely in its clinical manifestations and severity of symptoms. The first indication that a case of pneumonia may be due to a viral agent is frequently the failure to respond to antibiotics or chemotherapy. Not infrequently, the clinical picture is further complicated by the presence of a mixed infection consisting of both a viral agent and a superimposed bacterial invader. Such cases of mixed infections are peculiarly indigenous to the pediatric age group. Furthermore, the hypothesis has been advanced by some investigators that primary atypical pneumonia may be caused by the synergistic action of bacteria and some unknown virus.[8]

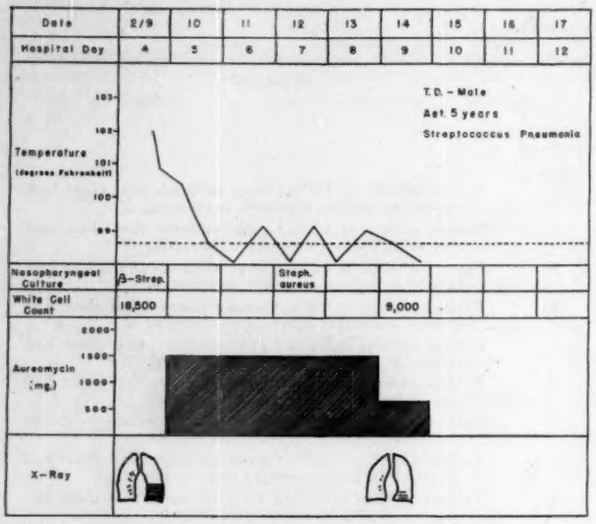

Figure 2. *Clinical Course and Laboratory and X-Ray Findings in T. D.*

Arbitrarily, the diagnosis of atypical viral pneumonia in our series was predicated on the history of cough, fever and physical and roentgenologic demonstration of pulmonary involvement, together with such laboratory aids as significant cold hemagglutination and streptococcus MG titers with normal white-cell counts. In a negative sense, the absence of pathogens from the nasopharynx as well as the lack of an adequate response to sulfadiazine or penicillin, or both, constituted additional evidence of a viral pneumonia.

Regarding the serologic phenomena associated with viral pneumonia, Horsfall[8] reported that 55 per cent of cases will show a positive cold hemagglutination reaction in a significant titer of 1:40 or above within two to four weeks of the onset of the illness. This investigator has also shown that streptococcal MG agglutinins in titers of 1:20 or above appear within the third to the fifth week in 50 per cent of cases of viral pneumonia. Unfortunately, this investigation was performed primarily on adults. Whether infants and children show the same serologic response has not been conclusively demonstrated since there is a paucity of well controlled studies in the literature. It should be noted that in view of the fact that confirmation of the diagnosis of viral pneumonia from serologic studies

Table 4. *Summary of 9 Cases of Viral Pneumonia Treated with Aureomycin.*

Case No.	Patient	Age	Temperature	Severity	Location	Nasopharyngeal Cultures	Cold Agglutinins	Streptococcus MG Titers
		yr.	°F.					
1	R. W.	5	102.4	Moderate	Right (bronchopneumonia)	*N. catarrhalis*; *Staph. albus* (hemolytic).	1 wk.–1:4 2 wk.–1:128 6 wk.–1:256	Negative
2	M. W.	11	101.0	Mild	Left lower lobe	*Staph. aureus* (nonhemolytic)	1 wk.–1:64 3 wk.–1:256 4 wk.–1:128	3 wk.–1:10 4 wk.–1:20
3	P. M.	11	101.0	Mild	Right upper lobe	Streptococcus (hemolytic)	1 wk.–negative 2 wk.–1:64	2 wk.–1:20
4	D. L.	9	105.2	Marked	Right upper lobe	*Staph. aureus* (hemolytic); *Bacillus subtilis.*	1 wk.–negative 3 wk.–1:2048 5 wk.–1:256	1 wk.–1:10 3 wk.–1:640 5 wk.–1:320
5	T. S.	2 7/12	101.6	Moderate	Right (bronchopneumonia)	Streptococcus (nonhemolytic)	1 wk.–negative 3 wk.–negative	3 wk.–1:40
6	C. H.	4	104.0	Mild	Right and left (bronchopneumonia)	*Staph. albus* (hemolytic)	4 wk.–1:16	4 wk.–negative
7	D. N.	1 3/12	103.0	Marked	Right and left (bronchopneumonia)	*Staph. aureus* (nonhemolytic)	1 wk.–1:64 2 wk.–negative	1 wk.–negative 2 wk.–negative
8	A. B.	4	102.6	Mild	Right and left (bronchopneumonia)	*Staph. aureus* (hemolytic)	1 wk.–negative 3 wk.–negative	1 wk.–negative 2 wk.–negative
9	H. H.	3	102.4	Mild	Right and left (bronchopneumonia)	*N. catarrhalis*	1 wk.–negative 3 wk.–negative	1 wk.–negative 3 wk.–negative

*Intramuscular injection.
†Oral administration.

appears some two to four weeks after the onset of the illness, these procedures have diagnostic value only in retrospect.

The rationale for a trial of aureomycin in atypical viral pneumonia rests on somewhat tenuous ground in view of the lack of precise etiologic data regarding the nature of the disease. It is known that the drug is particularly effective against some viruses, principally of the psittacosis-lymphogranuloma-venereum group. However, against the viruses of influenza A and B, aureomycin has been found to exert no inhibitory effect in vitro. With the demonstrated ineffectiveness of penicillin and sulfonamide in atypical viral pneumonia, it was considered worth while to treat a series of these patients as part of our investigation of the general efficacy of aureomycin in pneumonias in children. Nine cases appeared to fall into the category of atypical viral pneumonia. In the 5 cases that fulfilled all the criteria, including serologic confirmation, the age range was two and a half to eleven years. The temperatures varied from 101 to 105°F. The illness was classified as severe in 1 case, moderate in 2 and mild in 2. None of the patients required oxygen.

Nasopharyngeal cultures consistently failed to reveal any pathogens. The white-cell counts varied from 7000 to 11,000. Four of the 5 patients had cold agglutinin titers ranging from 1:64 to 1:2048, whereas the streptococcus MG titers ranged between 1:20 and 1:640. It should be pointed out that 4 patients with bacterial pneumonia had titers of cold agglutinins above 1:64 at the time of admission. However, in contrast to the rising antibodies noted in atypical pneumonias, a drop in titer was usually observed in the bacterial group during the second and third weeks. This has been reported previously by Young.[9]

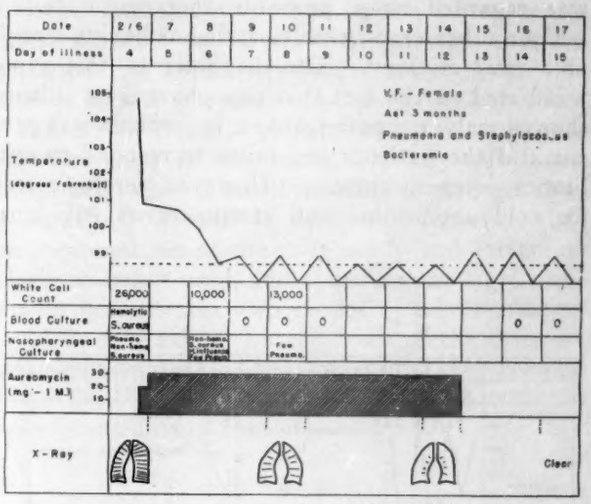

FIGURE 3. *Clinical Course and Laboratory and X-Ray Findings in V. F.*

Four of the 5 patients had had previous therapy without apparent benefit. Penicillin in therapeutic doses had been tried for at least three days, and in 2 cases chemotherapy had been used in addition.

TABLE 4 (*Continued*).

CASE NO.	MAXIMUM WHITE-CELL COUNT	PREVIOUS THERAPY	AUREOMYCIN THERAPY			RESULTS
			DAY INITIATED	DOSAGE	TOTAL DURATION	
				mg./kg./24 hr.	*days*	
1	9,500	Penicillin	9	30.0	6	Patient afebrile in 36 hr.; x-ray evidence of clearing in 8 days; recovery uneventful.
2	7,000	Penicillin; sulfadiazine.	8	50.0	6	Patient afebrile in 36 hr.; x-ray evidence of clearing in 7 days; recovery uneventful.
3	8,300	None	4	30.0	5	Patient afebrile in 24 hr.; x-ray evidence of clearing in 6 days; recovery uneventful.
4	18,200	Penicillin; sulfadiazine.	7	66.0	7	Patient afebrile 108 hr.; equivocal response; x-ray evidence of clearing in 13 days.
5	11,000	Penicillin; sulfadiazine	5	0.4* 25†	4 1	Patient afebrile in 18 hr.; x-ray evidence of clearing in 4 days; recovery uneventful.
6	8,100	Penicillin	5	45	5	Patient afebrile in 12 hr.; x-ray evidence of clearing in 7 days; recovery uneventful.
7	10,000	Penicillin	3	55	4	Patient afebrile in 24 hr.; x-ray evidence of clearing in 5 days; recovery uneventful.
8	3,500	Sulfadiazine	6	52	5	Patient afebrile in 60 hr.; x-ray evidence of clearing in 9 days; recovery uneventful.
9	6,400	None	6	60	5	Patient afebrile in 24 hr.; repeat roentgenograms not taken; recovery uneventful.

Aureomycin therapy was instituted from four to nine days after the onset of illness. Four of the patients showed a favorable response and became afebrile thirty-six hours after therapy was started.

Roentgenologically, however, the pneumonic process was found to resolve more slowly than in the cases of bacterial pneumonia. The fifth patient (who is described below in detail) required four and a half days for defervescence, and this case was regarded as a probable therapeutic failure.

Four other cases were classified as having a probable viral etiology. The diagnosis in this group was based on the fact that nasopharyngeal cultures showed only nonpathogens, a leukopenia was present and the patients had failed to respond to antibiotics or chemotherapy. However, serologic tests for cold agglutinins and streptococcus MG anti-

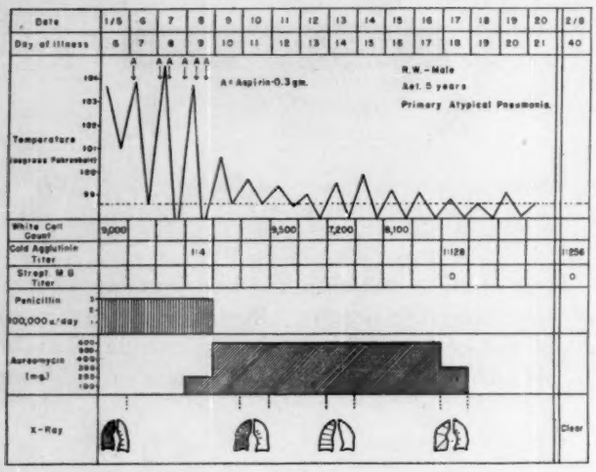

FIGURE 4. *Clinical Course and Laboratory and X-Ray Findings in R. W.*

bodies were negative. No attempts were made to isolate a viral agent. Each of these four cases showed a relatively good response to aureomycin therapy, with defervescence within thirty-six hours and clearing of the pneumonic process roentgenologically within five to eight days.

Details of the 9 cases with viral pneumonia are summarized in Table 4.

The following case is representative of the patients with atypical viral pneumonia who responded favorably.

R. W., a five-year-old Negro boy, was well until 5 days before admission, when he began to cough. Two days later he began to vomit and had an elevation of temperature. These symptoms persisted until admission to the hospital.

Physical examination revealed an acutely ill boy with mild dyspnea. The temperature was 102.4°F. The tonsils were enlarged and injected. There were dullness and tubular breathing over the third to fifth interspaces anteriorly on the right, and dullness and increased breath sounds below the left scapula.

The white-cell count was 9000, with 80 per cent neutrophils. Blood cultures taken on the 1st and 2nd hospital days were sterile. *N. catarrhalis* and hemolytic *Staph. albus* were cultured from the nasopharynx. X-ray study of the chest revealed a diffuse infiltration throughout the entire right side of the chest suggestive of bronchopneumonia and an increase in bronchovascular markings throughout the left side of the chest. The cold agglutinin titer on admission was 1:4; however, on the 18th day, it had risen to 1:128 and on the 40th day, the titer was 1:256. The clinical course and other pertinent data are shown in Figure 4.

The patient was given 300,000 units of procaine penicillin in oil intramuscularly daily for 4 days. However, the temperature remained elevated, ranging from 102 to 104°F. and there was no clinical improvement. Penicillin was discontinued, and on the 4th hospital day, aureomycin therapy was instituted; 100 mg. was given orally every 2 hours for three doses and then every 4 hours for a total of 5.1 gm. over a period of 6 days. Twelve hours after the initiation of therapy the temperature returned to normal and remained so except for a transitory elevation to 100.6°F. on the following day. The child improved rapidly, and the chest findings gradually returned to normal. Roentgenologically the lesion resolved rather slowly but finally cleared within 8 days.

The patient was discharged in good condition on the 16th hospital day. He remained well at home and was found to be in good health when seen in the follow-up clinic 3 weeks later.

The case of a patient with atypical virus pneumonia who failed to respond to aureomycin was as follows:

D. L., a 9-year-old girl, was admitted to the hospital with a nonproductive cough of 7 days' duration accompanied by slight anorexia but little or no fever. When she became febrile 4 days later, sulfadiazine had been started; however, her toxicity had progressed, necessitating admission to another hospital. Combined penicillin and sulfadiazine administered over a 3-day period appeared to be of little benefit, and the patient was transferred to the Children's Hospital for aureomycin therapy.

Physical examination revealed an acutely ill girl with a temperature of 105°F. orally and respirations of 35 per minute. Positive findings were limited to the chest, which showed

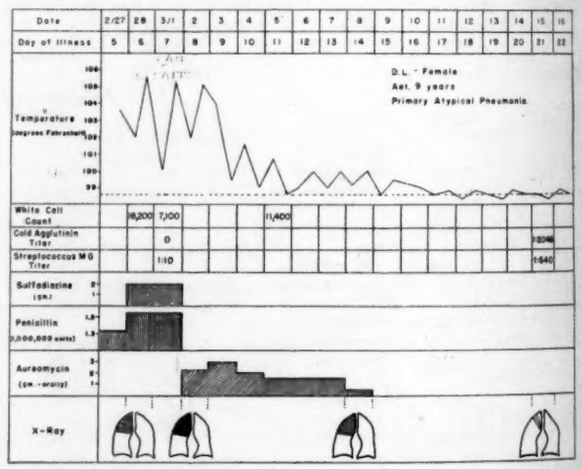

FIGURE 5. *Clinical Course and Laboratory and X-Ray Findings in D. L.*

a dullness and suppression of breath sounds over the right upper lobe.

Examination of the blood disclosed a red-cell count of 4,100,000, with a hemoglobin of 12.5 gm., and a white-cell of 7100, with 84 per cent neutrophils, 4 per cent of which were segmented. Urinalysis was essentially normal. A nasopharyngeal culture grew out hemolytic *Staph. aureus*. Cold

agglutinins on admission were negative; however, on the 21st day of illness a titer of 1:2048 was demonstrable. Streptococcus MG titer, which was 1:10 on admission, had risen to 1:640 on the 21st day. Roentgenograms revealed an area of homogenous density involving the entire right upper lobe. A repeat film 1 week later showed a gradual decrease in the opacity. The clinical course and other data are shown in Figure 5.

Aureomycin was started in a dosage of 500 mg. every 4 hours by mouth for 3 days and was then reduced to 250 mg. every 4 hours. The patient gradually improved, the temperature falling by lysis over a 5-day period with daily elevations. The toxicity subsided slowly over the same period, but on physical examination there was little change.

It is difficult to attribute any beneficial effect to aureomycin in this case. It was believed that a spontaneous remission was the more likely explanation for this child's slow improvement.

Dosage and Mode of Administration

Aureomycin was administered both orally and intramuscularly in this series. Oral medication alone was given to 25 patients. Nine received the drug intramuscularly, and 5 received it by both routes (but not simultaneously).

Whenever possible, the drug was administered in capsules. In the younger patients who were unable to swallow capsules the contents were emptied, and one of the following vehicles was used (depending on the likes and dislikes of the child): chocolate syrup, cherry syrup, applesauce, strained pears, lemon juice, orange juice, chocolate milk and jello. For the most part both infants and children accepted the aureomycin in spite of its disagreeable taste.

The daily dose in the patients with bacterial pneumonias who were given oral medication ranged from 40 to 100 mg. per kilogram of body weight per day, with an average of 63.5 mg. The patients with viral pneumonias received 25 to 65 mg. per kilogram of body weight per day, with an average of 45.5 mg. It should be pointed out that the latter group was composed largely of older children. No special attempt was made to calculate a precise dose of the drug on a weight basis. The drug was given orally in divided doses at an interval of four to six hours. The intramuscular dosage varied from 3.0 to 12.0 mg. per kilogram per day, with an average of 6.5 mg., the drug being administered at eight-hour intervals.

Aureomycin exhibited no untoward reactions aside from those referable to gastrointestinal irritation. The triad of nausea, vomiting and diarrhea occurred in 2 patients, whereas occasional vomiting without diarrhea was observed in 5.

In the determination of the time that elapsed before the patients became afebrile, a significant correlation was observed between the rapidity of defervescence and the mode of drug administration. Of the 13 infants and children who received intramuscular injection of aureomycin, 4 had a temperature drop to normal in less than thirty-six hours, and the temperature in 9 became normal after thirty-six hours. In comparison, 22 of the 26 orally treated patients had a normal temperature in less than thirty-six hours, whereas only 4 cases required more than thirty-six hours. Several of the infants treated by the intramuscular route showed tender, indurated buttocks, and this may have been a factor in the persistence of fever. It was our impression that the oral mode of administration of aureomycin was superior to the intramuscular in its clinical effect in this series; hence, the intramuscular route was discarded early in the study, and thereafter employed only when it was impossible to give the drug by mouth. It is well to point out, however, that comparable doses of the drug orally and intramuscularly were not used, and therefore any rigid comparison between the two modes of administration would be untenable. Larger doses of the drug intramuscularly were not employed primarily because of the greater severity of local reactions with increasing amounts of the drug.

Summary

Aureomycin was used in the treatment of 39 cases of pneumonia in infants and children.

In the 30 cases of bacterial pneumonias treated with the drug, the results were considered good in 24, fair in 5 cases and poor in only 1. The results were particularly good in pneumococcal pneumonia. Twenty-eight of the thirty patients were afebrile within seventy-two hours of initiation of aureomycin therapy.

In the 9 cases of viral pneumonia treated with aureomycin, all but 1 case were considered to have been favorably affected by the drug although the response was somewhat less striking than that observed with bacterial pneumonia.

Aureomycin was found to be more effective clinically when given orally than when given intramuscularly.

No toxic effects were observed in this series except for the occasional occurrence of nausea, vomiting and diarrhea.

We are indebted to Sara Stevens, B.S., M.T., and Mrs. Sarah Gouge for their technical assistance, to Phyllis Allred, R.N., and Lucie Knies, R.N., for their help in the compilation of statistics and to Dr. Harold W. Bischoff for the diagrams.

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DEVELOPMENT OF TOLERANCE TO ERGOT ALKALOIDS IN A PATIENT WITH UNUSUALLY SEVERE MIGRAINE*

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ERGOTAMINE tartrate (Gynergen) and the closely related dihydroergotamine methylsulfate (D.H.E. 45) appear to be the most successful pharmacologic agents yet proposed for the treatment of migraine attacks. Careful study of the properties and liabilities of these agents is justified by the fact that they may become irreplaceable in the treatment of very severe migraine unless the risks of narcotic addiction or intracranial surgery are to be assumed. It seems worth while, therefore, to report a case in which tolerance to these drugs developed and to describe the heroic measures that subsequently became necessary to control the patient's pain.

When properly administered in adequate dosage, early in the headache phase of the attack, ergotamine tartrate will rapidly terminate the attack in from 80 to 90 per cent of patients with migraine. The mechanism of its action depends upon its capacity to constrict dilated cranial arteries.[1] Dihydroergotamine is less effective in stopping headache, probably because it is a less vigorous cranial vasoconstrictor. When these drugs were compared, from 1 to 4 mg. of dihydroergotamine was required to reproduce the relief of headache offered by 0.5 mg. of ergotamine tartrate. Successful therapeutic amounts of these drugs often produce unpleasant toxic side-effects, such as nausea, vomiting, general lassitude, muscle cramps and transient vascular spasms. The problem, therefore, becomes one of finding, by trial and error, a dose of ergot alkaloid that will relieve headache with as few of these undesirable sequelae as possible. A few patients who tolerate ergotamine tartrate poorly will be relieved of headache by dihydroergotamine without disabling side reactions. Since the successful action of these drugs in relieving headache depends on their power of producing prolonged constriction of particular arteries, it is obvious that they should not be used in patients already suffering from obliterative vascular disease. Reports of several cases of ergotism that have occurred in patients receiving ergotamine for the relief of itching in jaundice[2-4] suggest that the liver plays an important role in excreting or detoxifiying this substance and that the presence of liver damage is a contraindication to its use. Ergotamine tartrate should not be employed during pregnancy because of its oxytocic effect, and although dihydroergotamine is reputed to be less powerful in this respect, it should not be used in pregnancy until more is known of its effect on man.

If the contraindications listed above are observed, there seems to be no reason why parenteral doses equivalent to 1.0 cc. (0.5 mg.) of ergotamine tartrate should not be given as often as every other day to patients suffering from migraine. Daily, 1.0-cc. (0.5 mg.) doses of ergotamine have been taken with impunity over a period of several years by a few patients,[5] but the reports of Cleveland[6] and Isenstead[7] suggest that, with doses of this frequency and amount, ergotism may possibly arise in otherwise healthy patients. Thus, if the daily administration of ergot derivatives becomes necessary, the patient should be forewarned and followed closely by the physician.

The minimum dose of ergotamine adequate to relieve headache, when once determined, ordinarily remains approximately constant from year to year even when the course of the disease requires frequently repeated administration. A patient of one of us has, for example, received ergotamine parenterally on an average of twelve to fifteen times each month over the past ten years. In 1938, this patient required 0.4 mg. of ergotamine to relieve each migraine attack, but in 1948, 0.25 mg. was equally effective although the headaches, if left untreated, apparently were not less severe. The unpleasant side-effects likewise usually remained just as active with the passage of time as they were with the first few doses. Most migraine sufferers, therefore, may count on the effectiveness, both therapeutic and toxic, of ergot derivatives through the years.

In the case reported below tolerance to both the therapeutic and toxic effects of ergotamine tartrate and dihydroergotamine methylsulfate developed rapidly after a long period of satisfactory response to normal dosage. The loss of effectiveness of these agents, and the relative ineffectiveness of other medical measures, ultimately necessitated neurosurgical intervention to control pain. This appears to be the first reported case in which tolerance to ergot derivatives has developed.

CASE REPORT

A young woman had been in good health apart from severe migraine, which had its onset in 1938 at the age of 20. The headache was right sided on all occasions; no headaches originated on the left side, although the pain spread across

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the midline if a severe attack was not treated promptly. Attacks were sometimes preceded by visual symptoms and were occasionally associated with nausea. Striking vascular phenomena were associated with the attack. These included generalized pallor before the headache and palpable pounding pulsation of peripheral arteries, particularly the right facial and right temporal arteries, during the headache. The family history was positive for migraine and for gout.

The patient received no ergotamine tartrate until the fall of 1942. During the spring and summer of that year the frequency of migraine attacks increased from an average of one attack every 2 or 3 days until they were recurring daily. In July, 1942, an episode of status hemicranialis necessitated hospitalization. A ventriculogram performed at this time was normal. An electroencephalogram in 1942, and again in 1947, showed some minor abnormalities, more prominent on the left side (the side opposite the headache) but no localizing signs were present. Arteriography was not carried out during the 1942 admission but an arteriogram in 1947 was normal.

Figure 1 shows the average monthly requirement of ergotamine tartrate (Gynergen) required for the relief of headache from the time its use was initiated in 1942, until it was finally discontinued in 1947. When dihydroergotamine methylsulfate (D.H.E.45) was introduced, attempts were made to substitute this agent because of its lesser toxicity. It was found that 2 cc. (2 mg.) of dihydroergotamine could be substituted for each 1 cc. (0.5 mg.) of ergotamine, but that doses of dihydroergotamine adequate to relieve headache generally produced the same unpleasant side-effects as adequate doses of ergotamine—namely, some nausea and a single short episode of vomiting. Substitution of dihydroergotamine for ergotamine was also attempted several times during the period in which tolerance developed, and it became apparent that tolerance for the two agents was developing simultaneously and at the same rate. The headache was not relieved when 0.5 mg. of ergotamine was replaced by 0.2 mg. of ergonovine.

In the fall of 1942, when the patient first received ergotamine, the clinical response was most gratifying, and was followed by a decrease in the frequency of attacks to one every 4 days. Later that year and in early 1943, attacks occurred even less often, but they increased in frequency with the return of warm weather. During the winter of 1943–1944, the patient enjoyed a 2 months' complete remission, but again the headaches recurred with warmer weather and they gradually increased in frequency and in severity.

Attacks were particularly severe during the summer of 1946. Beginning in May, 1946, headaches recurred daily. At first, they were well controlled by single daily injections of 0.5 mg. of ergotamine tartrate, but in July, 1946, larger single doses were required and the attacks recurred as frequently as twice or three times a day. Only on a single day from May, 1946, until 20 months later was headache ever completely absent. During this period and during the following months, the patient's peripheral vascular status was examined before each injection of ergotamine, but no evidence of the development of peripheral vascular insufficiency was ever noted.

From July, 1946, until its use was interrupted in January, 1947, the amount of ergotamine required to control symptoms increased more or less continuously along the logarithmic curve shown in Figure 1. In the final weeks of its use, its efficacy became so slight that the administration of the required large intramuscular injections presented a real problem. Individual doses of 7 cc. (3.5 mg.) of ergotamine tartrate or of 12 cc. of dihydroergotamine methylsulfate (12.0 mg.—equivalent to 3.0 mg. of ergotamine) were given four times during the first 12 days of January, 1947; 10-cc. doses of dihydroergotamine were also given on eight occasions during this period. The largest total daily dose was given on January 10, 1947, when the patient received 13 cc. of ergotamine tartrate and 39 cc. of dihydroergotamine methylsulfate over a 24-hour period; a dosage of alkaloid equivalent to 16.3 mg. of ergotamine tartrate. During the entire month from December 12, 1946, until the use of ergot derivatives was discontinued on January 12, 1947, the patient received 331 cc. of ergotamine tartrate and 398 cc. of dihydroergotamine methylsulfate, administered intramuscularly in 115 individual doses.

Small doses of ergotamine tartrate, 0.5 mg. every 2nd or 3rd day, were again given during a period of attempted medical therapy in July and August, 1947, after external-carotid ligations had proved unsuccessful. These doses were without effect on the headache. On October 1 a single intravenous infusion of 15.0 mg. of dihydroergotamine methylsulfate was given over a period of 6 hours. The procedure was uneventful for the first 5½ hours but was discontinued in the last ½ hour, when the patient complained of muscle cramps in both legs. This was accompanied by a fall in skin temperature and obliteration of the left dorsalis pedis pulse for 3 days. The left femoral and popliteal pulses were present throughout.

Since it became apparent not only that the headaches were more frequent but also that ergotamine was less effective, trials of many of the other current nonoperative treatments of migraine were undertaken. One hundred per cent oxygen gave partial relief in milder attacks but was the only agent to do so to a significant degree apart from narcotics and the vasoconstrictor analgesics of the ephedrine-benzedrine group. Attempts to uncover and to treat allergic hypersensitivity to histamine or environmental agents and a fifty-hour trial of psychoanalytic psychotherapy were likewise ineffective. No medical measures had any real degree of efficacy. Ligation of the right external carotid artery relieved pain partially for a short time, but the intensity of the pain began to increase 3 weeks postoperatively and soon had returned to its preoperative severity. Ligation of the left external carotid artery, ligation of the right middle meningeal artery and avulsion of the greater superficial petrosal nerve were entirely unsuccessful.

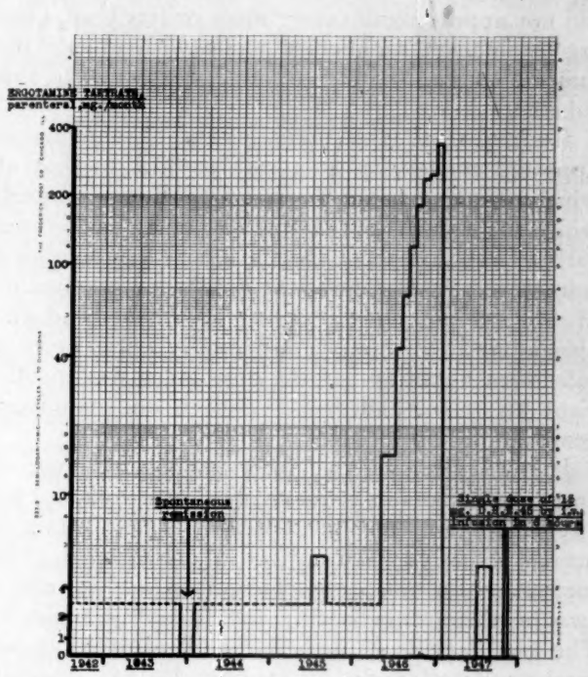

FIGURE 1. *Average Monthly Requirement of Ergotamine Tartrate in a Patient with Unusually Severe Migraine.*

The dotted lines indicate periods for which the data are approximate. When supplementary D.H.E. 45 (dihydroergotamine methylsulfate) was given, 4 mg. was considered the equivalent of 1 mg. of ergotamine tartrate. The dosage of 5 mg. a month in July and August, 1947, did not relieve headache.

During this period, when ergotamine was losing its effectiveness, and subsequently when its use was stopped, and until the patient finally received neurosurgical relief, meperidine hydrochloride (Demerol) was required in increasing amounts to control pain, finally reaching a level of 3.0 gm. subcutaneously per day. It was discontinued without withdrawal symptoms after the pain was relieved.

The patient was completely relieved of headache by a section of the posterior root of the right trigeminal nerve performed at the Massachusetts General Hospital on December

23, 1947, by Dr. James C. White. At the time of writing, she has been completely free of headache for over a year.

Discussion

In the case reported above, a striking resistance to large doses of ergotamine tartrate developed. During the development of this refractory state, resistance to other ergot alkaloids occurred. Thus, at various points during the phase of developing tolerance, it was possible to show, by substitution of dihydroergotamine methylsulfate for ergotamine tartrate in a ratio of 4 mg. to 1 mg., that dihydroergotamine was equally effective (or, later, ineffective). Under these conditions, dihydroergotamine did not appear significantly more or less toxic than ergotamine. A number of trials with ergonovine maleate showed that refractoriness extended to this substance as well.

Resistance to the toxic effects of ergotamine appeared to develop at a rate parallel to that at which resistance to the therapeutic action developed, which suggested that the drug was being inactivated rather than that the cranial arteries were becoming refractory. At all times, the dose of ergotamine or of dihydroergotamine necessary to relieve headache also induced some nausea and usually a brief episode of sudden vomiting. If the dose given was insufficient to relieve headache, nausea and vomiting generally did not occur.

It is not clear whether interruption of the use of ergot derivatives in January, 1947, was followed by any significant return of sensitivity. Certainly, normal sensitivity did not return, as shown by the ineffectiveness of 0.5 mg. of ergotamine given every two or three days during the following summer. The vascular effects of the large dihydroergotamine methylsulfate infusion of October 1, 1947, suggest that there had been some return of sensitivity. This must have been slight, however, since the infusion was tolerated at a rate of 2.5 mg. per hour for over five hours before any effects were noted.

Summary

What appears to be the first reported case of the development of tolerance to ergot alkaloids by a patient with migraine is reported. After three and a half years of typically satisfactory clinical response to the usual doses of ergotamine tartrate, tolerance to this agent developed rapidly and extended to dihydroergotamine methylsulfate and to ergonovine maleate as well. Refractoriness to the emetic and vascular effects of these agents developed concurrently with tolerance to the therapeutic effect. Withdrawal was not followed by a return of normal sensitivity within nine months.

During the period in which tolerance developed, most other medical measures currently used in the treatment of migraine were given trials. None were significantly successful. Surgical section of both external carotid arteries, of the right middle meningeal and right temporal arteries and of the right greater superficial petrosal nerve were ineffective. Complete relief of headache was finally obtained by surgical section of the posterior root of the right trigeminal nerve.

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LOCALIZED PRETIBIAL MYXEDEMA*

A Stigma of Hyperthyroidism

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THE term "myxedema" is frequently used as a synonym for "hypothyroidism." It is a matter of common experience, however, that the majority of patients with clinical hypothyroidism do not have either local or generalized mucinous changes in the skin. Local myxedema in euthyroid persons is a familiar entity to the dermatologist. Such lesions usually are not symmetrically placed and appear singly or multiply on the upper or lower extremities or on the trunk. Definite, local, myxedematous changes may also occur in patients with exophthalmic goiter. A few reviews[1-4] and scattered case reports[5-24] have appeared. The concurrence of hyperthyroidism and local myxedema is not coincidental since all reported cases have this association. When local circumscribed lesions of myxedema have been described in hyperthyroid patients, they have, with rare exceptions, always been bilateral on the lower legs.

The gross appearance of the skin lesion is characteristic. Elevated plaques or nodules of thickened skin are present, well demarcated from the surrounding normal skin. The involved area is darker than that around it and is often yellowish pink. The hair follicles are wide and deep, producing a "pigskin" appearance. On palpation, the lesion is firm and cool, and it does not pit on pressure. Although the anterior tibial regions are always involved, extensive lesions may surround the lower leg. Symptoms arising from these areas are few. Mild, tingling pruritus or numbness may occur. Patients often complain of the unsightliness of their legs. If a biopsy is made, clear white viscous material escapes from the incision.

Histologic section reveals little change in the epidermis. In the corium the fibroelastic tissues separate into individual strands between which is a homogeneous, mucin-staining material. Occasional spindle cells are seen in this matrix. Lymphocytic infiltration around some of the smaller blood vessels is present. Pillsbury and Stokes[6] examined all types of local myxedema and found them histologically indistinguishable. Watson[2] used hyaluronidase to incubate biopsied skin in his 2 cases. He obtained equimolar fractions of two polysaccharides and concluded that the mucinous material was hyaluronic acid, chondroitin sulfuric acid or mucoitin sulfuric acid. He ran similar tests on normal pretibial skin and found much less of this substance.

The lesion appears at variable times, either concurrently with the developing exophthalmos and other thyrotoxic signs and symptoms or after incomplete ablation of the toxic thyroid gland. Hyperthyroidism may be recurrent. In 69 cases reviewed by Trotter and Eden[1] the lesions appeared before treatment of the hyperthyroidism in 32, after x-ray therapy in 2 and after subtotal thyroidectomy in 35. Of the last group, 11 first showed the skin lesion during a recurrence of thyrotoxicosis. In 3 cases reported by Netterton and Mulvey[7] lesions developed with a recurrence of thyrotoxicosis after operation — 2 during postoperative hypothyroidism and 1 sixteen years after a second thyroid operation. In a collection of isolated case reports most lesions appeared either preoperatively or with the reappearance of toxicity after partial resection.

Once present, local pretibial myxedema runs a slow and unpredictable course. Dunhill[8] saw clearing of the lesions in 6 of his 7 cases after partial thyroidectomy, but this has not been the experience of others. The established lesion is not influenced by thyroidectomy, iodine or thiouracil derivatives. Complete remissions, without evidence of change in thyroid status, occur in some cases. Excision of the involved skin was performed occasionally for a cosmetic effect.[5] In all cases in which the status of the eyes was mentioned, exophthalmos had been present at some time.

The incidence of this syndrome cannot be stated with less than 100 cases reported. Trotter and Eden[1] found it in 3 per cent of 130 cases of hyperthyroidism. Isolated short case reports have recently appeared,[11-24] most of them as a part of the proceedings of meetings of dermatologic societies that are not listed in the *Quarterly Cumulative Index Medicus*.

Various terminologies have been suggested. Cohen,[4] in a recent review, proposed the term "myxedema circumscriptum thyrotoxicum." This suggests that the syndrome is a definite entity and indicates its nature.

CASE REPORT

H. I. B., a 27-year-old married Navy veteran, apparently well until October, 1945, had noted gradual onset of increased perspiration, progressive loss of weight, voracious appetite, emotional lability and prominence of the eyes. He continued to sleep well, had no gastrointestinal disturbances and carried

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on with his duties. By late December he had lost 38 pounds of weight and was aware of a rapid heart beat. Examination at that time revealed an enlarged thyroid gland and the presence of exophthalmos. The basal metabolic rate was +55 per cent. The patient was started on Lugol's solution and was flown to the United States for definitive treatment. When his basal metabolic rate had fallen to +14 per cent a subtotal thyroidectomy was performed. The postoperative course was

FIGURE 1. *Lesions of Circumscribed Pretibial Myxedema.*

stormy. For several weeks he lost the sight of his right eye and had much impaired vision of the left. Although the eyes became exceedingly prominent he had no pain. Gradually the eyesight returned to its previous value, but exophthalmos continued. In March, 1946, he was sent East with the basal metabolic rate at + 6 per cent. During the next 14 months he convalesced at the United States Naval Hospital at Chelsea, Massachusetts. There was a complete remission of all toxic symptoms, except exophthalmos, and he was discharged from the service.

At the time of his transfer to Chelsea the patient first noticed elevated, pink, painless areas of skin over the shins (Fig. 1). They gradually increased in area but changed little if any in the months prior to admission to the Veterans Administration Hospital. A biopsy of one of the skin lesions was made at the Naval Hospital and reported as showing typical myxedema (Fig. 2).

In the fall of 1947 the patient noted a return of his former toxic symptoms, including a weight loss of 14 pounds despite a large appetite. The basal metabolic rate at this time was +37 per cent. He was given propylthiouracil, 100 mg. a day, for several weeks. The basal metabolic rate fell to +14 per cent but the drug was omitted because of a blood smear, which showed fewer than 50 neutrophils per cubic millimeter. For this reason the patient was admitted to the Veterans Administration Hospital in April, 1948.

Physical examination revealed a well developed and well-nourished man in no distress but restless, constantly moving his hands and body. Under the right sternomastoid muscle was a firm mass, 5 by 5 cm., which moved with swallowing and appeared to be thyroid tissue. No thyroid gland was palpated on the left. Marked bilateral exophthalmos was present (Fig. 3), and the lids could not be closed. Pupillary reaction was normal, and fundoscopic examination was negative. The heart was not enlarged; a regular sinus rhythm and a soft apical blowing systolic murmur were present. A fine tremor of the outstretched fingers was noted. Over each shin (Fig. 1) were raised plaques, sharply demarcated, erythematous but not pitting. The hair follicles were wide and deep; the skin elsewhere was normal.

The blood pressure was 120/84, with a moderate tachycardia.

The blood serologic findings were negative, and a complete blood count was normal. The total serum cholesterol was

FIGURE 2. *Photomicrograph of a Skin Biopsy Taken from a Pretibial Lesion of the Same Patient. (The Slide was Kindly Lent for this Purpose by the United States Naval Hospital, Chelsea, Massachusetts.)*

161 mg., with esters of 73 mg. per centimeter. A urinalysis was negative, with a specific gravity of 1.030. Subsequent white-cell counts were 7900 and 8400, with 65 per cent and 55 per cent neutrophils respectively. X-ray examination of the chest was negative. An electrocardiogram was normal except for low T waves in Lead V5.

The patient remained afebrile. After preliminary studies he was given 200 mg. of propylthiouracil a day, the dosage

being increased in a few days to 300 mg. a day. The basal metabolic rate steadily declined from +43 to +4 per cent in 30 days. During this period the patient underwent complete remission of all symptoms except those related to his exophthalmos and the pretibial myxedema. He gained weight regularly and was permitted to return to his on-the-job training as a color matcher in a paint factory. No changes in the eyes or in the leg lesions were noted at a follow-up examination 6 months later.

FIGURE 3. *Extreme Exophthalmos of the Patient Whose Skin Lesions Are Illustrated in Figure 1.*
At the time the photograph was taken all other signs of thyrotoxicosis were well controlled with propylthiouracil.

SUMMARY

The syndrome of exophthalmic goiter and bilateral pretibial myxedema is a distinct entity. This distribution of local myxedema is seen only in patients with past or present thyrotoxicosis. Histologically such skin lesions are indistinguishable from other types of myxedema.

A typical case of the syndrome is reported.

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COMPARATIVE STUDY OF FORMULA PROCESSING FOR OBSTETRIC NURSERIES*

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OUTBREAKS of diarrhea of the newborn in hospital nurseries have in recent years caused a great deal of needed emphasis on improving the technic of nursery care and of formula preparation. To study this entire problem the American Academy of Pediatrics set up a committee on the fetus and newborn infant, and this committee has in turn created subcommittees in various states.

The committee for Massachusetts[1] made specific recommendation taken from the New York Sanitary Code for the guidance of hospitals in formula preparation. This recommendation is as follows:

> Formulae and other fluids offered to newborn infants in hospitals or child caring institutions, or in maternity hospitals or maternity homes shall be poured into individual feeding bottles at the time of preparation, and a nipple shall be attached to each bottle and covered with a cap. The entire product shall be then subjected to terminal heating by steam under pressure at not less than 15 pounds . . . for not less than 5 minutes, or at a pressure of not less than 6 pounds . . . for not less than 10 minutes, or by flowing steam at a temperature of not less than 100°C. (212°F.) for not less than 30 minutes. . . .

At the time this recommendation appeared, the hospital where the studies given below were made, was preparing the formulas in accordance with the directions published by the American Sterilizer Company,[2] whose apparatus§ the hospital was using. These directions were as follows:

> Terminal Disinfection of Formulas.
>
> Step 1. Following preparation, the formulas are immediately placed in sterilizer and disinfected by non-pressure steam for 15 minutes at 180°-200°F. The period of exposure is timed when the thermometer indicated 180°F. in its advance toward the maximum. Exposure continues for 15 minutes, no longer, after which the steam is turned off and the door opened immediately. The usual 15-17 pounds pressure should be maintained in the jacket of the sterilizer.
>
> Step 2. Remove formulas from sterilizer and allow to cool at room temperature for approximately one to two hours. Finally, transfer formulas to refrigerator maintained at a temperature of 20° to 36°F. where they remain until feeding time.

Since this procedure was at variance with the recommendation of the Massachusetts Committee on the Fetus and Newborn Infant, a question was raised about the future policy of the hospital regarding formula processing. It was consequently decided that a comparative study be made of the three alternative methods suggested by the Committee and the method directed by the American Sterilizer Company.

Two types of formula were tested, both of which were in current use in the hospital. One consisted of commercial evaporated milk, karo and water, and the other was identical except for the substitution of Grade A milk with 2 per cent fat content. These two formulas were tested in all four ways, both before and after contamination with pathogenic organisms. The bacterial counts were made according to the standard "American method" for milk analysis. Transplants were made in suitable mediums (endo and blood agar) to test survival of pathogenic organisms added to the formulas before processing. The results of these tests are shown in Table 1–4.

For the sake of brevity in these tables only average results are shown. In all, 97 different observations were made with a minimum of 3 readings in any given test. In the tests summarized in Table 1–3 utensils were clean but not sterile. In the procedure summarized in Table 4 utensils and containers were sterilized.

TABLE 1. *Pressure–Steam–Disinfection Method — 15 lb. for Five Minutes.**

COLONIES BEFORE PROCESSING *per cc.*	COLONIES AFTER PROCESSING *per cc.*
Evaporated-milk formula:	
29,000	0†
48,000	0‡
38,000	0§
Contaminated specimen (*Escherichia coli* and hemolytic streptococcus):	
310,000	0‡
	120§
Modified 2 per cent milk formula:	
34,000	0†—0‡—0§

*In all casea a thick coagulum formed in the formulas and the nipple shields became adherent to the nipples.

†After immediate refrigeration for 24 hr.

‡After 1 hr. of cooling and 24 hr. of refrigeration.

§After 3 hr. of cooling and 24 hr. of refrigeration.

TABLE 2. *Pressure–Steam–Disinfection Method — 6 lb. for Ten Minutes.**

COLONIES BEFORE PROCESSING *per cc.*	COLONIES AFTER PROCESSING *per cc.*
Evaporated-milk formula:	
38,000	0†—0‡—0§
Contaminated specimen (*Esch. coli* and hemolytic streptococcus):	
380,000	0‡—0§
Modified 2 per cent milk formula:	
17,000	0†—0‡—0§

*In all cases a thick coagulum also formed in the formulas, and the nipple shields became adherent to the nipples.

†After immediate refrigeration for 24 hr.

‡After 1 hr. of cooling and 24 hr. of refrigeration.

§After 3 hr. of cooling and 24 hr. of refrigeration.

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§Formula sterilizer-disinfector-cylindrical (open mounted, steam heat).

Summary and Conclusion

Formulas before and after bacterial contamination were tested by four methods of processing.

Steam pressure at 15 lb. for five minutes gave adequate protection in all cases but demonstrated clearly the practical disadvantage by the formation of a thick coagulum with the subsequent plugging of nipple holes and the adhesion of the nipple to the paper nipple covers.

Steam pressure of 6 pounds for ten minutes gave exactly the same result.

Flowing steam for thirty minutes at 212°F. gave adequate protection even of grossly contaminated formulas, provided refrigeration was begun within an hour of processing. Moreover, no coagulation formed.

Flowing steam at 180 to 200°F. for fifteen minutes did not guarantee bacterial safety of the formulas.

It is therefore concluded that flowing steam for thirty minutes at 212°F., since it provided a safe product bacteriologically and did not cause the disadvantage of a coagulum, is the method of choice.

Table 3. *Flowing-Steam-Disinfection Method — 212°F. for Thirty Minutes.**

Colonies before Processing per cc.	Colonies after Processing per cc.
Evaporated-milk formula: Not tested	0†—0‡
Contaminated specimen (*Esch. coli* and hemolytic streptococcus): 382,000	50†—250‡ (no pathogenic organisms)
Modified 2 per cent milk formula: Not tested	0†—0‡

*No coagulum formed, and the nipple shields did not become adherent to the nipples.
†After 1 hr. of cooling and 24 hr. of refrigeration.
‡After 3 hr. of cooling and 24 hr. of refrigeration.

Table 4. *Flowing-Steam-Disinfection Method — 180 to 200°F. for Fifteen Minutes.*

Colonies before Processing per cc.	Colonies after Processing per cc.
Evaporated-milk formula: Not tested	0*—330†
Contaminated specimen (*Esch. coli*, *Proteus vulgaris* and hemolytic streptococcus): 295,000	10,000†
Modified 2 per cent milk formula: 20,000	1900†

*Immediately after processing.
†After 1 to 3 hr. of cooling and 24 hr. of refrigeration.

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MEDICAL PROGRESS

GASTROINTESTINAL ALLERGY*

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GASTROINTESTINAL allergy is a diagnosis frequently entertained, occasionally evaluated and rarely established. It offers, to its enthusiastic supporters, a reasonable explanation for many obscure abdominal complaints. To the skeptical, it frequently appears as a specious and unwarranted diagnosis. Although these conflicting views cannot be resolved on the basis of existing knowledge, the present status of gastrointestinal allergy is examined in this review with the hope of separating the well founded from the hypothetical.

The term includes reactions occurring in the sensitized gastrointestinal tract as a result of contact with an allergen, whether the allergen is an ingested food or reaches the gut after inhalation or injection. Although foods are considered to be the most important cause of such reactions, food allergy should be distinguished from gastrointestinal allergy. Food allergy includes any allergic reaction due to an ingested food, whether the reacting site is in the gut or elsewhere.

The number of gastrointestinal complaints that have been ascribed to allergy make up a formidable list, which includes heartburn, epigastric pressure, fullness, bloating, belching, nausea, vomiting, distention, aches, cramps and colics, constipation, diarrhea, fecal mucus, blood in stools and even jaundice.[1-3] Allergy has also been suggested, at one time or another, as a cause of nearly all gastrointestinal diseases of obscure origin, particularly peptic ulcer[4,5] and ulcerative colitis.[6-8] To summarize each of the articles supporting allergy as a cause of gastrointestinal disorders would present the reader with a tedious sequence of detail that

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would confuse rather than clarify the subject. In many reports, the material presented is insufficient, either to confirm or to discount whatever causative role is assigned to allergy. It appears preferable, therefore, to emphasize the methods used to demonstrate and diagnose allergic reactions of the gastrointestinal tract rather than to list opinions that are frequently conflicting. The measures used to demonstrate gastrointestinal allergy fall into three major categories: experimental studies, clinical observation and laboratory tests.

Experimental Studies

Experimental procedures do not provide conclusive evidence for the spontaneous occurrence of allergic reactions in the human gastrointestinal tract, but they do indicate that the gut, animal or human, may be the site of an allergic reaction causing recognizable local changes or disorders of function.

In sensitized dogs and rabbits, gastric ulcers were produced by Shapiro and Ivy[9] after the injection of the antigen into the gastric mucosa. Ulcers in the stomach and duodenum were likewise caused in dogs by Friesen et al.[10] using a special technic. An antiserum prepared against five antigens was injected into the gastric or duodenal wall or into the left gastric artery to induce local passive sensitization to the five antigens. Each of these was then injected into the systemic circulation on successive days to produce repeated allergic reactions in the sensitized area. Local edema without cellular reaction or eosinophilic infiltration was readily produced and was most marked two to six hours after injection of an antigen. Ulcers developed in some animals but were more frequent when the injections of antigen were associated with the administration of histamine in beeswax.

Although highly artificial, these experiments show that marked allergic reactions similar to those occurring elsewhere, notably the skin, may be produced in the gastrointestinal tract of animals. The circumstances in these experiments differ from those obtaining clinically in that injection was used for both sensitization and to elicit the allergic response. Experiments in guinea pigs have shown that systemic anaphylactic sensitization and the appearance of circulating antibody may follow ingestion of certain foods, such as milk[11] and egg white.[12] Sensitization arises, presumably, because the ingested antigen is absorbed into the circulation. In studies with egg white[12] prolonged feeding finally led to apparent failure of the antigen to traverse the gastrointestinal barrier. The antibody titer, having risen during the early feedings, fell during continued feeding, but quickly rose again when egg white was given by injection. The parallel between these observations and the well known tendency of children to outgrow clinically recognizable food allergies is obvious. Leaving the more remote implications of these studies aside, there is clear evidence that the experimental animal may develop antibody and systemic anaphylactic sensitivity to antigens taken by mouth. However, these observations do not bear directly on gastrointestinal allergy because changes in the gastrointestinal tract itself were not seen. Furthermore, the circumstances of the experiments were again artificial because the antigens fed the animals were not normal constituents of the diet.

A closer experimental approach to the clinical aspects of gastrointestinal allergy is to be found in the work of Walzer and his co-workers.[13, 14] They injected serum obtained from a subject highly sensitive to peanut into the skin of the arm and into the mucosa of the rectum[13] and the intestine in patients with ileostomy and colostomy.[14] Introduction of peanut into the lumen of the bowel gave rise to edema at the sensitized sites in the skin and intestine at nearly the same time. Reactions in both sites also occurred when the peanut antigen was applied only to the sensitized site in the rectum or intestine. They considered that absorbed allergen reaching the sensitized site by way of the blood stream was primarily responsible for the reaction:

> It was noted that, on rectal administration of the antigen, the edema at the sensitized (rectal) site began to develop slowly. This reaction preceded the lighting up of the control site on the skin by as much as six minutes. With the appearance and development of the cutaneous reactions the edema and erythema at the rectal site became more intense and rapidly reached its height.

They concluded that the local reaction "may be induced by antigen which is in direct contact with it or by absorbed antigen which reaches it via the circulation or by both."[13]

To these observations may be added the rare cases of abdominal pain, cramps, or diarrhea following overdosage during treatment of asthma or hay fever with injections of allergenic extracts. Especially significant is the much more frequent occurrence of nausea, vomiting, cramps, and diarrhea in persons being treated with pollen extracts by mouth.[15-17] In these cases gastrointestinal symptoms were closely correlated with the administration of the allergen. Although the allergic nature of these symptoms need hardly be doubted, control studies were not done to rule out nonspecific irritation of the bowel.

These observations lead to the conclusion that under suitable circumstances marked allergic reactions *may* occur in the gastrointestinal tract; that systemic sensitization may be produced by ingestion of an allergen; and finally that the gastrointestinal mucosa may be sensitized with skin-sensitizing antibody (allergic reagin) and will react with edema on contact with the allergen, especially if this reaches the site by way of the blood stream.

Clinical Observations

Since gastrointestinal allergy includes a wide variety of complaints and exhibits no characteristic syndrome, the diagnosis cannot be made on the basis of symptoms per se. The majority of those who believe in the prevalence of gastrointestinal allergy consequently depend upon an apparent relation between the ingestion of a suspected food and the subsequent onset of symptoms. To some, the patient's say-so is sufficient. Thus, Andresen[2] believes that many medical mistakes have been made when the physician ignores a patient's observation that his symptoms follow the ingestion of certain foods, and, in studying the chronology of allergic symptoms, Alvarez and Hinshaw[18] considered it sufficient to select their subjects on the basis that these patients "knew that the ingestion of certain foods regularly caused distress." In the opinion of others,[19-22] the patient's incrimination of specific foods must be accepted with caution.

Even if the patient has correctly identified a certain food as the cause of his gastrointestinal symptoms, this correlation does not prove the existence of gastrointestinal allergy. Food intolerances of other origin must be considered.[20] Assuming that allergy does play a role, the gastrointestinal manifestations are not necessarily primary but could conceivably stem from an allergic reaction taking place elsewhere in the body. For example, gastrointestinal symptoms of all types might be caused by the intensely disagreeable sensations associated with the induction of severe asthma following the ingestion of certain foods.[23]

Corroboration of impressions gained from the patient's history is frequently sought by the giving or withholding of the suspected food. If symptoms are invariably precipitated when a certain food is eaten, or conversely if they disappear on elimination diets, the culpability of the food seems to be demonstrated. Procedures of this type have consequently been used in many clinical studies that have attempted to establish the diagnosis of gastrointestinal allergy. Although the rationale of various elimination or provocative diets is similar, the technics of applying these measures vary in the hands of different allergists. The details of dietary tests are well expounded in the writings of Rowe,[22] Vaughan,[24] Randolph,[25] and Rinkel.[26]

Three major difficulties beset the diagnosis of gastrointestinal allergy as made by correlating symptoms with the eating of certain foods. In the first place, any patient's response is influenced by subjective attitudes that are difficult to exclude. Secondly, the attributes of gastrointestinal allergy are so all-inclusive that it emerges as a hazy entity with ill defined margins. Finally, neither the execution nor the interpretation of dietary tests is easy. These difficulties may now be considered in more detail.

Many physicians, aware of the emotional and situational forces that condition man's attitude toward food, accept the patient's incrimination of specific foods with reservation. Representing this point of view, Metzger[27] writes "If a fear or fixed idea concerning roses or goldenrod can, and apparently does precipitate a condition which is or resembles hay fever, why then is it not logical to assume that definite fears of needles, milk, and a host of other things react in the same way? Phobias and fixed ideas are common in the neurotic." Results obtained by elimination or provocative diets may also be compromised by uncontrolled factors. Precipitation of symptoms by administration of a food to which the patient believes himself sensitive involves psychic factors sufficiently powerful to complicate the whole test. The dominant influence that such factors may exert has been demonstrated by Wolf,[28] who showed that even the well established pharmacologic effects of a drug like atropine can be inhibited or reversed by the patient's attitude and expectations. Similarly, the apparent success of an elimination diet is hard to differentiate from the success any regimen may enjoy in the treatment of functional disorders, particularly if the regimen embodies considerable dietetic ritual and is administered by an enthusiastic physician who obviously has the patient's welfare at heart.

A fair evaluation of the effect of elimination diets in the therapy of organic disease poses comparable difficulties. In treating chronic ulcerative colitis, for example, careful observers[6, 7] insist upon removing from the diet foods that they believe play an allergenic and etiologic role. In their opinion, milk is a prime offender. Yet equally experienced physicians do not hesitate to use milk as a staple in their dietary management of ulcerative colitis. As long as ulcerative colitis remains a disease of obscure etiology, responding with approximately equal but incomplete success to a number of conflicting regimens, the etiologic implication of any therapeutic principle must be accepted with caution unless a specific relation between treatment and response is undeniable. For similar reasons, the beneficial effects claimed for elimination diets in the treatment of peptic ulcer[4, 29] are hard to evaluate.

When testing patients with foods to which sensitivity is suspected, one may reduce psychic factors by giving the test substance under carefully controlled conditions that prevent the patient from knowing, by sight, taste, texture, smell or any other means, what food is being given. The possibility of error in the diagnosis of gastrointestinal allergy is underscored by our experience with patients who are "clinically" sensitive to common foods but who failed to manifest any gastrointestinal symptoms whatever upon ingesting the suspected substances.[30] A twenty-year-old girl, for example, stated that she could not eat fish because it caused vomiting and asthma; even getting near a fish market caused

these symptoms. Skin reactions to fish were strongly positive. However, a freshly prepared fish extract, also causing a marked skin reaction of the immediate type, was introduced into the stomach by stomach tube in a manner to prevent the patient from knowing that fish was being introduced. No symptoms occurred, and there was no change in the stomach or small intestine recognizable by fluoroscopy. Furthermore, no delayed symptoms occurred.

If gastrointestinal allergy were a well defined entity with respect to etiology, chronologic sequence, reaction and reproducibility, the information obtained from the patient's history and test diets would be far more conclusive. If, for example, the ingestion of a certain amount of a specific food always produced the same symptoms within a certain interval, psychogenic and allergenic disorders could be differentiated quite satisfactorily. Unfortunately, as the following paragraphs indicate, the characteristics claimed for gastrointestinal allergy are extremely variable.

Alvarez and Hinshaw[18] state that an offending food may be recognized because symptoms regularly follow its ingestion within a period of one to twelve hours, and usually within three hours. Others, however, do not subscribe to this viewpoint and maintain that sensitivity to foodstuffs may be variable, intermittent, cumulative, nonquantitative and characterized by unpredictable time relations.[2, 23, 29, 31] Some believe that a patient's sensitivity may vary because of climate, season, dietary habits, intercurrent infection, endocrine activity, emotional states or spontaneous immunologic fluctuations.[6, 22, 32, 33] It has also been suggested that food may contain seasonal contaminants[33] (pollen in milk, for example), thereby explaining an inconstant relation between symptoms and ingestion of the suspected agent. According to Vaughan,[34] a food may be eaten with impunity for days until a cumulative effect brings about symptoms. Others[25,35] believe just the opposite: if an allergenic food is eaten often enough, the allergy may be "masked," and a clear reaction may only be seen if ingestion of the food is preceded by a period of elimination. The interval between eating of a suspected food and ensuing symptoms may also be affected by the site of the sensitized gastrointestinal tissues and by the effects of digestion. The stomach, for example, might react within a few minutes of eating, but, unless the allergen is bloodborne, the colon might not be affected for forty-eight hours. The effects of digestion are disputed. Olmsted et al.[36] recommend as nonallergic a diet consisting principally of protein digests (amino acids and polypeptides) glucose, and vitamins. On the other hand, the products of protein digestion[36-39] and even glucose[25] have been suggested as possible allergenic agents. If polypeptides, "proteoses,"[40] and "propeptans"[41] are responsible for gastrointestinal allergic manifestations, the onset of symptoms will obviously depend on the rate of digestion.

From a practical viewpoint, elimination diets are difficult to apply. Since allergy to minute quantities of food is believed possible,[22, 25] the patient must exercise great care to avoid even the smallest quantity of any food, condiment or drink that is prohibited. Some patients are either too ignorant or too careless to follow such meticulous regimens. Others, dependent upon the processed foods so extensively used today, violate rules innocently. Even the cornstarch paste used in sealing cardboard food containers may, according to Randolph,[6] contaminate the contents sufficiently to cause symptoms of gastrointestinal allergy. Whatever the reason, the success of an elimination diet is frequently threatened by its practical difficulties, particularly if a patient is believed to be sensitive to several foods.

Interpretation of many of the reported cases in which trial diets were applied to the diagnosis of gastrointestinal allergy is difficult because particulars are omitted. Although it is often stated that symptoms disappear after removal of a food, the duration of the symptom-free period may not be given. If symptoms persist during allergic management, their recurrence is usually attributed to unwitting ingestion of the incriminated food, evidence for which is sought by the most detailed and laborious history taking. That this may lead to serious error can be readily appreciated when it is realized that equally detailed histories may not be taken when the patient is well. Thus, repeated exposure to the allergen without development of symptoms is not excluded. On the other hand, when the patient eats the incriminated food with impunity, the discrepancy is often explained away by a number of assumptions, such as the existence of masked allergy, desensitization by repeated exposure, and refractory periods.

The tendency of more than one allergic manifestation to occur in patients with rhinitis, asthma, eczema and hives has led to the view that gastrointestinal symptoms occurring in such cases are often allergic in origin. However, the allergic nature of the reactions in the skin or respiratory tract is not always established beyond a reasonable doubt. In many cases of asthma, eczema and hives, demonstration of a causative allergen is difficult, and such manifestations are sometimes considered allergic chiefly because their clinical characteristics are similar to those in which the operation of an antigen-antibody reaction may be considered settled. Thus, a personal or family history of asthma, urticaria or eczema in a patient with gastrointestinal symptoms or abnormalities merely suggests an allergic tendency but in no way establishes the diagnosis of gastrointestinal allergy. Furthermore, gastrointestinal symptoms are so common that they may arise from a variety of causes even in patients with an un-

doubted allergic background. Bockus[43] believes that "Anxiety and tensional states, psychoneuroses, neurosis, vegetative and endocrinal disturbances, dietary and hygienic faults, and organic diseases account for abdominal symptoms in allergic persons much more commonly than do allergic reactions per se." Hence, a personal or family history of symptoms suggesting allergy does not appear to be a very reliable criterion when the role of allergy in either functional or organic gastrointestinal disorders is considered.[4, 5, 44]

At times, gastrointestinal disorders are part of a syndrome originally described by Willan[45] ("purpura associated with violent vomiting, excruciating pain in the bowels, and anasarcous swelling of the legs, thighs, and hands") but now often referred to as the Schönlein-Henoch syndrome. Attacks of this type were described in 29 patients by Osler[46-50]: visceral symptoms were usually associated with erythema, urticaria, angioedema, or purpura, but an occasional attack consisted of purely gastrointestinal disorders. Of the many patients with Schönlein–Henoch syndrome that have been reported since Osler's description, a few have been subjected to operation because of symptoms suggesting an acute condition of the abdomen. Abdominal pain in these cases must have been striking, but the operative findings have been inconstant. At times, the intestine has been edematous,[38] more often hemorrhagic,[51] but frequently its appearance has been normal.[52] Because some of the features of the Schönlein–Henoch syndrome resemble serum sickness, Osler[50] wrote, in typical style, "Before long the anaphylactic key will unlock the mystery of these cases." This suggestion has been readily accepted as an established fact, and Osler's cases are frequently cited as examples of gastrointestinal allergy.

Although Osler[46] stated that "the attack bears no relation whatever to food," several subsequent reports have ascribed this syndrome to food allergy.[19, 53-59] In some of these cases specific allergies may actually have been responsible for the Schönlein–Henoch syndrome. However, in most cases the relation of the symptoms to the alleged food allergen is not clear-cut. The interval between ingestion of the food and onset of symptoms ranges when given from fifteen minutes to nine days; in many cases the follow-up period appears inadequate, and in not a single case was the food given in a manner such that the patient was unaware of its nature.

Davis,[60] in reporting 44 cases of Schönlein–Henoch syndrome, did not consider food, drugs or other known allergens as the cause but emphasized that the attack frequently followed a hemolytic streptococcus infection. Similar observations were made by Gairdner,[61] who, on the basis of his own cases and a review of the literature, suggested that the syndrome is linked clinically, pathologically and etiologically with acute nephritis, rheumatic fever and polyarteritis nodosa. The syndrome of purpura, urticaria and gastrointestinal symptoms, it is apparent, may be a manifestation of hypersensitivity, but evidence that it is caused by ingestion of allergenic foods is inconclusive.

In a number of cases suffering from abdominal pains believed to be allergic in origin, an injection of epinephrine has been followed by relief within thirty minutes. This effect has been held to substantiate the allergic nature of the complaint.[62, 63] That epinephrine might alleviate gastrointestinal allergy as it relieves asthma and urticaria is a reasonable hypothesis. On the other hand, a sympathomimetic agent like epinephrine may be transiently spasmolytic as well. Relief of nonallergic symptoms by epinephrine is a possibility that detracts from its use as a therapeutic test in the diagnosis of abdominal allergy.

In summary, the diagnosis of gastrointestinal allergy by clinical means depends principally upon the patient's incrimination of specific foods, the effect of trial diets and association of the gastrointestinal complaints with manifestations usually believed to be allergic. Analysis of these criteria reveals them as quite unsatisfactory. The reliability of trial diets, theoretically the best of these diagnostic measures, is impaired by the expectations and the attitudes of the patient and by difficulties in execution and interpretation, but most of all by the vague nature of gastrointestinal allergy itself. A clear-cut, if tentative, definition of what constitutes gastrointestinal allergy must be made before the clinical diagnosis of this condition can achieve precision.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 35341

PRESENTATION OF CASE

A twenty-two-year-old unemployed laborer entered the hospital because of visual difficulties.

The patient grew normally until the age of about thirteen years, when he realized that he was not as tall as other children. After fifteen years he stopped growing in height altogether. At the time of entry he measured 5 feet, 3 inches. His hat size was 7⅛ and his shoe size No. 8. He never developed axillary hair. He occasionally had erections and nocturnal emissions. Seven years before entry he first noticed that he had a squint, the left eye turning out. At the same time he began to have severe headaches, which were usually "behind the eyes" and lasted from several hours to a day. They had become less frequent during the past year or two. Three years before entry the patient began to complain of inability to see well to either side. Because of this he bumped into things, particularly on the left. The patient did well in school and finished the second year of high school, after which he had to go to work. He supported himself as a laborer. His only complaint aside from his eyes was a chronically poor appetite.

Physical examination showed a patient who appeared more like an adolescent boy than a man of twenty-two years except for a peculiarly old facies, with wrinkles about the eyes and mouth. His head was disproportionately large, and the extremities seemed too long for the body. The neck was short. Except for scanty growth of pubic hair, the skin was smooth and hairless. The skin of the distal phalanges was hard and shiny. The heart, lungs and abdomen were normal. The testes, penis and prostate were small. The left dorsalis pedis artery was not palpable. Both eyes were rather prominent. Vision was 20:20 on the right and 20:200 on the left. The left optic disk was pale; the right was normal. The left eye diverged about 25°, and the cranial nerves were otherwise normal. The musculature was somewhat underdeveloped, but there was good strength. Sensation was normal.

The temperature, pulse and respirations were normal. The blood pressure was 90 systolic, 70 diastolic.

The fasting blood sugar was 67 mg. per 100 cc. After 4.5 units of regular insulin, it was 26 mg. per 100 cc. in thirty minutes and 36 mg. in one hour. At that point 0.4 cc. of 1:1000 epinephrine was given intravenously. This was immediately followed by extreme anxiety, rapid pulse and pallor and a drop in blood pressure lasting about two minutes. The blood sugar curve was not affected and gradually returned to a level of 64 mg. per 100 cc. after a total of three hours.

The serum cholesterol was 320 mg., and the cholesterol esters 241 mg. per 100 cc.

The 17-ketosteroids in a twenty-four-hour urine sample were 0.4 mg.

The spinal fluid was normal with a pressure equivalent to 150 mm. of water and a total protein of 26 mg. per 100 cc. The basal metabolic rate was −22 per cent.

X-ray examination of the pelvis showed the epiphyses of the femoral heads to be closed. Those of the ilia were just closing. The epiphyses of the elbows, wrists and knees were closed but not fused. There was enlargement and destruction of the sella turcica. The posterior clinoids could not be traced, but in their stead there was an area of calcification extending upward for half an inch. A pneumoencephalogram showed the bodies of the lateral ventricles to be elevated and obliterated along the lower margin. The third ventricle appeared to be displaced backward. The aqueduct was somewhat erect. There was no dilatation of the lateral ventricles. The intelligence quotient was 107, and psychometric tests did not reveal any definite indications of brain disease.

On the fifteenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. BERTRAM SELVERSTONE: Like so many patients who do not mature normally because of anterior hypopituitarism, this young man had apparently come to accept himself as he was—different from others but not alarmingly so. He complained chiefly of visual difficulties, a "neighborhood symptom." The stigmas of failure of the anterior pituitary body are, however, clear. A deficiency of growth hormone had apparently been present since before the age of thirteen, at which time he first noted his shortness of stature. Sparse pubic hair, absent axillary hair and small genitalia point to early hypogonadotropic eunuchoidism. The disproportionate limb length suggests an associated delayed closure of epiphyses, and the roentgenograms of the long bones confirm this impression. Deficiency of thyroid

stimulation by thyrotropic hormone will explain the low basal metabolic rate and elevated serum cholesterol. There is evidence also of deficiency of the adrenocorticotropic hormone; the low arterial pressure and increased sensitivity of the blood glucose concentration to the administration of a small dose of insulin are important in this connection. Presumably, a severe impairment of glycogen storage in the liver was present, as shown by the failure of the lowered blood glucose to rise when a large dose of epinephrine was administered. We may consider this anomaly of carbohydrate metabolism to be a manifestation of deficiency in glucocorticoids, resulting also from lack of adrenocorticotropic hormone. The extremely low value for urinary 17-ketosteroids reflects the deficiency both in gonadotropic and in adrenocorticotropic factors. I should not consider abnormal the extreme cardiovascular and emotional response that resulted from the intravenous administration of 0.4 cc. of 1:1000 epinephrine. This was an unusually large intravenous dose and could well have produced these alarming symptoms in a normal person. The curious admixture of youth and senility in his appearance is a common feature of hypopituitarism. Perhaps Dr. Albright can tell us the precise endocrine basis of this phenomenon.

The manifestations that with respect to the pituitary body, we call "neighborhood symptoms" were apparently more important to the patient. It is not surprising that squint and headache were complained of for four years before he noted visual impairment, since an acuity of 20:20 was still present in the right eye at the time of admission. The headache is significant — it was not the bitemporal aching pain often present when the diaphragma sellae is stretched by an intrasellar tumor but was a pain "behind the eyes." This is suggestive of pressure on the tentorium, although pain may be referred to this region from other portions of the basal dura. The left external strabismus is suggestive of pressure on the oculomotor nerve although other manifestations of such pressure were not noted. Pressure from above, as by a herniated hippocampal gyrus, usually produces pupillary dilatation as a first sign of compression of this nerve against the free edge of the tentorium. The arrangement of fasciculi in the nerve is such that pressure from an anterior direction might well produce an early extraocular muscle weakness. Pressure on the third nerve at its entrance into the cavernous sinus, or even within the sinus, might also produce this picture. The patient complained for three years of inability to see well to either side, and apparently his symptoms were worse on the left side. The pale left optic disk, with 20:200 vision on the left, confirms the impression that this patient may have had originally a bitemporal hemianopsia, which later spread to include the macular field on the left. Unfortunately, objective determination of visual fields is not mentioned in the case summary. I think that we may say, however, that there was evidence of chiasmal compression, more marked on the left side. That the lesion was only slowly progressive is suggested by the normal psychometric examination and normal cerebrospinal fluid pressure.

We have, then, a young man who presents evidence of a lesion of at least nine years' duration, involving the basal dura, optic chiasm and possibly the left oculomotor nerve. The anterior pituitary had been progressively compromised, without evidence of impairment of posterior pituitary function.

A number of lesions in the region of the sella turcica can produce a clinical picture with some of the features presented by this patient. Although two or three earlier cases appear in the literature, chromophobe pituitary adenomas are usually not manifest until after the age of fifteen years. They do not produce the suprasellar calcification mentioned in the description of the roentgenograms. Glioma of the optic chiasm could be considered also, but preservation of even 20:200 vision in the left eye and normal visual acuity in the right after so long a period would be most unusual. Then, too, a severe endocrine disturbance is most uncommon with such lesions. Meningioma of the tuberculum sellae may occur at twenty-two but would be most unusual at thirteen years, when symptoms were first noticed. Endocrine abnormalities are usually not a feature of this tumor and an elevation of cerebrospinal-fluid protein would probably have been noted. Arachnoiditis of the optic chiasm could produce visual changes such as those described, but pituitary dysfunction is not a feature of the disease and calcification, if it occurs, is in a position anterior to that described. Curiously enough, occasionally in obstructive hydrocephalus, the floor of the third ventricle may be ballooned downward sufficiently to produce chiasmal compression and pituitary hypofunction. The normal cerebrospinal-fluid pressure and the pneumoencephalographic findings effectively rule out such a disorder.

A variety of hamartomas may occur in the midline at the base of the brain. Cushing* reported, in 1912, a case of Osler's in which a teratoma the size of a golf ball was found in the interpeduncular fossa of a sixteen-year-old seamstress. Dermoids and lipomas may also be seen. The cholesterol deposits of Hand-Schüller-Christian's disease characteristically affect the neurohypophysis rather than the anterior lobe. Chordoma of the basisphenoid should also be mentioned. Chordomas usually run a briefer course, but one such lesion of eighteen years' duration has been reported. Much more extensive destruction of the base of the skull would probably have occurred during the nine years of this patient's story, and a nasopharyngeal mass would have been likely as well.

If we proceed now to a more detailed consideration of the roentgenographic findings, we are led to

*Cushing, H. *The Pituitary Body and Its Disorders.* 341 pp. Philadelphia: J. B. Lippincott Company, 1912. P. 43.

a more common clinical entity. The description of enlargement of the sella turcica with an area of calcification extending upward from the region of the absent posterior clinoids is that of the cystic or solid tumor of a Rathke-pouch remnant variously called craniopharyngioma or adamantinoma. Such calcification is seen in 70 to 85 per cent of these lesions. The term "destruction" is used also in describing the sella. If true destruction, as opposed to erosion by pressure, was present, we must consider also the carcinoma, which occasionally arises in such a lesion. The description of the pneumoencephalogram is consistent also with craniopharyngioma, an unusually large one, extending under the frontal lobes and probably adherent to mammillary bodies, midbrain and pons as well. I cannot be certain whether the lesion was primarily cystic ("suprasellar cyst") or solid. The former would offer a much more favorable prognosis.

Clinical Diagnosis

Craniopharyngioma.

Dr. Selverstone's Diagnosis

Craniopharyngioma (adamantinoma) with secondary hypopituitarism.

Anatomical Diagnosis

Suprasellar epidermal cyst.

Pathological Discussion

Dr. Charles S. Kubik: Operation by Dr. William H. Sweet disclosed a cystic suprasellar tumor with a dense, fibrous capsule and contents consisting of yellowish, avascular, soft solid, flaky material, which was removed by spoon and suction, leaving an "enormous" cystic cavity. The material appeared to be typical of epidermoid cyst, not only on gross inspection but also microscopically, consisting of faintly outlined epithelial cells and containing cholesterin crystals. The cyst wall, of which only a small piece was removed, was composed of dense connective tissue. Although no epithelial lining was included with the biopsy specimen, the character of the flaky material removed left little or no doubt that this was a cyst lined with epidermal cells, sometimes also known as "cholesteatoma" and "pearly tumor." The flaky material consists of accumulated desquamated epithelial cells.

Epidermoid cyst of the region of the chiasm is considerably less common than craniopharyngioma, but we have had 2 or more other cases. In at least 1 of them there was a homonymous hemianopsia, and the tumor was on one side, as in this case. They may occur in other parts of the cranium and cranial cavity — for example, in the orbit, cerebellum, intercerebral fissure, temporal bone and other parts of the skull.

In this case the patient made a good recovery. His headache was relieved. The visual acuity of the left eye did not improve, and the homonymous hemianopsia persisted.

CASE 35342

Presentation of Case

A seventy-year-old Irish housewife entered the hospital because of extreme weakness.

Five weeks prior to admission she noted the onset of excessive weakness and "tiredness." Shortly thereafter she began to suffer continuous dull, aching, nonradiating, epigastric pain unrelated to meals. This was associated with mild nausea and occasional vomiting without hematemesis. Vomitus either was watery and sour or contained undigested food, depending on time relation to previous meal. There was mild loss of appetite. No irregularity of bowel habit was noted and the stools were free of blood. Two weeks prior to admission the urine became "red," and the stools light in color. A physician made a diagnosis of "yellow jaundice" for which "white pills" were prescribed. Weakness was progressive and finally required hospital entry after "her knees suddenly gave way" as she was walking about her house. Consciousness was not lost during this episode, nor were there any other symptoms referable to the central nervous system. There had been a 20-pound weight loss during the preceding three months. Moderate generalized pruritus was a troublesome symptom from the onset of the present illness.

Twelve years before entry she developed an indolent ulcer on the second toe of the left foot. She was found to be mildly diabetic but was rapidly standardized with a daily dose of protamine zinc insulin of 36 units daily. The toe was amputated, and the pathological report was acute and chronic osteomyelitis. From that time on she attended the Out Patient Department sporadically. The diabetes remained under good control without significant alteration in insulin requirement.

Physical examination disclosed an extremely obese, deeply icteric woman able to lie comfortably, flat in bed. The body weight was 215 pounds. Numerous cutaneous excoriations were prominent, but there was no superficial lymph adenopathy. The heart and lungs were clear. Minimal tenderness without muscle guarding was elicited in the right upper quadrant of the abdomen. The liver edge was palpable 15 cm. below the right midanterior costal margin "with the suggestion of another edge 5 cm. above the liver border." Owing to the patient's obesity it was impossible to determine the character of the liver or to establish the presence or absence of nodules. There was a minimal rectocele, but no masses could be palpated on digital examination. There was no edema of the extremities,

and pulsations were palpable over the dorsalis pedis and popliteal arteries. The Achilles and patellar reflexes were not elicited, but the biceps reflexes were active and equal.

The blood pressure was 130 systolic, 58 diastolic. The temperature, pulse and respirations were normal.

The urine was acid and the specific gravity ranged from 1.008 to 1.016. There was a + to +++ test for albumin. The urine contained sugar (green) on only one occasion. Many granular casts and leukocytes were noted in the sediment. Bile tests were ++++ at all time, but the urinary urobilinogen was negative. Examination of the blood showed a red-cell count of 3,900,000, with a hemoglobin of 12 gm., and the white-cell count ranged from 15,000 to 22,000 with neutrophils ranging from 84 to 92 per cent. The stools were pale and guaiac positive on two occasions. The blood sugar was 237 mg. and the nonprotein nitrogen 66 mg. per 100 cc. The cephalin-flocculation test was + in 24 hours and ++ in forty-eight hours; the lipase was 2.5 cc. The total protein was 5.51 gm. per 100 cc., with 2.83 gm. of albumin and 2.68 gm. per 100 cc. of globulin. The van den Bergh reaction was 20 mg. per 100 cc. direct and 24 mg. per 100 cc. indirect. The prothrombin time was 16 seconds (control 15 seconds). The carbon dioxide was 21.6 milliequiv. per liter; the phosphorus was 4.9 mg. per 100 cc., and the alkaline phosphatase 43.0 units per 100 cc.

Adequate fluoroscopic study of the gastrointestinal tract was impossible because of the patient's size and debility. On routine films the right leaf of the diaphragm was higher than usual but the lung fields were clear. The esophagus contained a tube but was otherwise not remarkable. No localized disease was detected in the stomach. There was a suggestion of a filling defect measuring approximately 2.5 cm. on the medial aspect of the second portion of the duodenum. The duodenal loop, however, did not appear enlarged. The liver shadow appeared enlarged.

Following admission the patient had no complaints other than weakness. She tolerated a soft diet well for twenty-four hours but then began to vomit all food eaten. For this reason food was withheld, and parenteral feedings were employed. A gastric tube was passed and left in position in order to aspirate barium following the gastrointestinal series.

On the fourth hospital day she became disoriented. On the following day she became stuporous, but the diabetes was considered under fair control. Her course was one of rapid deterioration. Coma supervened on the following day, and death occurred twenty-four hours later. During the last day of life the temperature rose to 101°F., the pulse to 100, and the respirations to 25.

Differential Diagnosis

Dr. Daniel S. Ellis: As I read this case over, it seemed to me fairly easy to make a diagnosis that would explain most of the reported findings.

Let us, for the moment, consider this patient's diabetes. This was of twelve years' duration. Apparently it was mild, of the type seen in elderly people, and was easily controlled although she had one gangrenous toe, which was amputated. She could possibly have gone into diabetic coma during the last few days of her life. But had she done so, I am sure that we would have had laboratory and clinical evidence of it. Next let us consider infection. I cannot find any real evidence of a chronic suppurative process. It is true that she had a high white-cell count, with a high neutrophil count. She was afebrile until the end. There is nothing else in the record to suggest any chronic suppurative process unless, perhaps, one is going to say that she had chronic pyelonephritis.

I am left with the problem of deciding whether or not this patient had obstructive jaundice due to mechanical block in the extrahepatic biliary tree or diffuse parenchymal disease of the liver. I believe very strongly that her death was due to disease in her liver; yet there is little evidence to make a diagnosis of diffuse parenchymal disease in the nature of hepatitis, cirrhosis or yellow atrophy. The cephalin-flocculation test, which I would expect to have been +++ or ++++ if the jaundice and liver disease had been caused by hepatitis or cirrhosis, was normal. The fact that she had no urobilinogen in the urine, although she had plenty of bile present, is strongly in favor of an obstructive type of jaundice. In addition, the patient had itching of three months' duration. If that were on the basis of parenchymal liver disease, hepatitis, cirrhosis or biliary cirrhosis, almost surely there would have been other laboratory evidence of such a condition. One frequently sees itching as a presenting symptom in obstructive jaundice, or of disease involving the liver or extrahepatic biliary tree, long before jaundice supervenes. So we have several findings very strongly in favor of an obstructive process: the long history and itching; the high alkaline phosphatase; the light-colored stools; and the lack of urobilinogen in the urine.

The x-ray report mentions something in the second portion of the duodenum. This is, of course, one of the places that we want to look at, and a gastrointestinal series should be done on all patients with unexplained jaundice, even though they have not had nausea or vomiting or anything else to point to gastrointestinal disease.

Dr. Wyman, will you show the x-ray films? I would like to be sure that this woman had some significant finding in the second portion of the duodenum.

DR. STANLEY M. WYMAN: The right leaf of the diaphragm is considerably elevated, and the liver appears considerably enlarged. The lung fields are not remarkable grossly. A gastrointestinal examination was done in the supine position only. I could not examine the esophagus because of the presence of a large tube, which one can see in the lower esophagus. The stomach itself was very large and contained retained fluid, but there was no evidence of gross intrinsic disease of the stomach. The duodenal loop was impossible to see well fluoroscopically, but there appeared to be a pressure defect of the second portion of the duodenum on its medial aspect, measuring perhaps 2.5 cm. in diameter. This is seen on one film well, is only suggested on this second film and is inadequately seen on this third film.

DR. ELLIS: Anatomically, is that where the ampulla of Vater is or where the common duct lies going through the duodenal wall?

DR. WYMAN: I think this area is in or about the ampulla of Vater. I thought she had a tumor of the ampulla, or distal common duct, or else a nonopaque stone. Examination, of course, was not ideal.

DR. ELLIS: To tie in with Dr. Wyman's findings, this woman had a positive guaiac reaction on the stools. The nausea and vomiting were not necessarily due to any lesion in the stomach or gastrointestinal tract. They may have been caused by the severe disease that I am assuming she had in the liver or in the biliary tract somewhere. There is nothing to suggest an increase in the width of the duodenal loop due to a carcinoma of the pancreas.

As Dr. Wyman has told you, we have no evidence of intrinsic disease in the stomach itself.

I cannot make any case for an extremely fatty liver, other than the fact that she was obese. We are not told of any alcoholic history. One of the things that can cause this picture of deep jaundice, a sudden and progressive onset to fatal outcome, is an acute fatty alcoholic liver in which no normal cells, or practically none, are observed in histologic sections. The liver may be large, and the skin deep orange. The history may not suggest it at all. The laboratory tests at that time may be so equivocal and the process so relatively acute that they have not had a chance to reach the point where they would show evidence of parenchymal disease. This is just a possibility that I must think about and that must be ruled out. It would be of help to have had an aspiration biopsy from the liver. It might have revealed whether or not she had diffuse fatty infiltration of the liver or metastatic disease in the liver.

This patient may have had a pylephlebitis due to some focus of infection of which I am not aware. I will do no more than mention that as a possibility. I cannot rule out the presence of lymphomatous disease.

I really believe that this woman had metastatic carcinoma involving the liver. That is the one condition, or one of the conditions, that will give a tremendous liver and a high alkaline phosphatase. The question is: Where did the carcinoma come from? It could have come from the stomach. There is one suggestion that there was a mass on top of the mass of liver. It is pointed out in the protocol that the mass was felt 5 cm. above the margin of the liver. One wonders if the mass was gall bladder and the upper mass was the liver edge. The x-ray studies do not indicate carcinoma of the stomach. Therefore, I cannot hold to that diagnosis.

Carcinoma of the head of the pancreas frequently metastasizes to the liver. It may metastasize to the porta hepatis, without metastasizing elsewhere, and cause obstructive jaundice. If this was such a case, I cannot explain the tremendous size of the liver reported.

Could this patient have had gallstone? She certainly could. If so, it was a silent stone and apparently in the common duct if the jaundice was due to it.

We are now left having to explain her death and her large liver. I would not think she had been sick long enough, or had jaundice long enough, to cause her death if all this was on the basis of simple obstruction. For that reason, I believe that this woman had a carcinoma of the biliary tract, probably in the common duct or ampulla of Vater, and that she had metastases all through the liver, producing hepatomegaly and leading to hepatic failure. Metastases in the liver frequently do not manifest themselves until the patient is almost in a terminal stage. I think that her sudden death was due to extensive involvement of the liver by cancer. The blood in the stools was probably on the basis of an ulcerative tumor of the common duct or the ampulla of Vater. In a certain number of cases, however, deeply jaundiced patients may have guaiac-positive stools without any ulcerative lesion.

The protocol reports albumin and granular casts and some cellular elements in the urine. This in a woman seventy years might simply be a finding that one frequently sees in an arteriosclerotic person who is extremely ill. I suppose, because of the large number of cellular elements, I have to say that there was some factor of pyelonephritis here, but I find it hard to say that that was any more than a concomitant finding and it did not play a part in the terminal episode.

Carcinoma of the biliary tract, probably arising in the common duct or ampulla, with metastases to the liver, was my first impression to explain this case. I still stick to it and am fully prepared to find out that something existed that I have not mentioned. The x-ray report of a deformity in the region of the ampulla leads me to exclude primary hepatoma as a possibility.

Clinical Diagnosis

Carcinoma of ampulla of Vater.

Dr. Ellis's Diagnoses

Carcinoma, biliary tract.
Extensive and diffuse metastases to liver.
Diabetes mellitus.
Generalized arteriosclerosis.
Arteriosclerotic kidneys — ? pyelonephritis.

Anatomical Diagnoses

Carcinoma of gall bladder.
Thrombosis of hepatic and portal veins, neoplastic.
Massive infarction of liver.
Intercapillary glomerulosclerosis.
Cholelithiasis.
Neurofibroma of esophagus.
Carcinoma of right breast.

Pathological Discussion

Dr. Tracy B. Mallory: Autopsy showed a liver filled with carcinoma as Dr. Ellis had suspected. It took a little longer to clear up the question of the primary site. There was no tumor at the ampulla of Vater. There was a shallow benign peptic ulcer in the duodenum, which was probably responsible for the blood in the stools. The gall bladder was greatly enlarged and was obviously the edge that was clinically interpreted as liver, whereas the second "edge," 5 cm. higher, was the true liver margin. There was a large stone impacted in the ampulla of the gall bladder, and the walls of the gall bladder showed papillary excrescences and one rather large necrotic mass that could have been inspissated secretion or totally necrotic tumor. There was no doubt that the carcinoma arose in the gall bladder.

One of the surprises of the autopsy was that the veins throughout the liver, both portal and hepatic, were extensively thrombosed. There was massive secondary infarction of liver substance. The thrombus from the hepatic vein had extended up into the inferior vena cava in a form that could be called Chiari's disease. These thrombi consisted in large part of fibrin and platelets but also had many tumor elements in them. Hepatomas, of course, commonly invade the hepatic vein. It is rare for a tumor arising in the gall bladder, as we are sure this one did, to do so, but it is not impossible.

We found a number of coincidental lesions. There was a small intraductal carcinoma of the right breast, which had not produced metastases. The esophagus contained a submucous neurofibroma of significant size, 1.5 by 3 cm., which had apparently produced no symptoms, and there was a colloid adenoma of the thyroid gland.

The patient was enormously obese and deeply jaundiced, and post-mortem examination was delayed for fourteen hours so that post-mortem decomposition was severe and microscopical sections are not of very much help. We did, however, think that we could recognize enough in the kidney to say that she had the Kimmelstiel–Wilson type of glomerular change that is so commonly seen in advanced diabetes. There was slight pyelonephritis. I do not believe either lesion was responsible for any significant symptoms and death was explained first by carcinoma and secondly by acute liver insufficiency and liver necrosis, dependent on a massive thrombosis of the veins throughout the liver substance.

Dr. Ellis: I think it is amazing how far cancer of the liver, especially metastatic, can go before it is recognized. I did not bring out the fact, as Dr. Mallory has done, that the terminal episode is frequently due to some such processes as occurred here.

Dr. Benjamin Castleman: How large was the liver?

Dr. Mallory: It weighed 3500 gm.

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IMPROVED BLUE SHIELD BENEFITS

The Blue Shield program in Massachusetts has undergone recent changes, some of which will widen its scope and all of which should increase its value.

A surgical-obstetrical but nonmedical contract will be reissued to compete with the low-cost surgical-obstetrical contract now issued by commercial insurance companies. It is unfortunate that internists are at present excluded from participating in this part of the Blue Shield program, but in this instance price, and not benefits, is the determining factor.

Both the new surgical-obstetrical and the present medical-surgical-obstetrical contracts will be offered to nongroup subscribers, who are not eligible for group enrollment. Two years ago contracts were offered to nongroup subscribers, but the difficulties toward which Blue Cross was at that time headed forced the suspension of nongroup enrollment in both organizations. As of September 1, 1949, nongroup enrollments will be available to every healthy applicant in the Commonwealth.

A change in subscription rate will be rendered necessary by this new policy. The yearly subscription rate of $29 per family has been found insufficient to cover the losses sustained on families in the nongroup and conversion categories. The conversion category consists of those subscribers who leave their place of employment, about half of whom allow their insurance to lapse. Many of the remainder retain their coverage because of the anticipation of medical care. Consequently the rate for these two categories only will go from $29 to $32 per year.

Certain clarifications have been made in the provisions of both surgical-obstetrical and medical-surgical-obstetrical contracts. Benefits will be provided for the care by a pediatrician of a premature baby weighing four and a half pounds or less. Benefits will not be provided for the circumcision of an infant during the first year of life, as such an operation is practically never a surgical necessity.

A member who uses private accommodations in a hospital when private accommodations are not medically necessary and ward accommodations are available, becomes thereby a limited or overincome member, subject to an additional charge by the attending physician. It is believed, however, that the profession should exercise extreme caution in availing itself of this provision.

A one-year waiting period will go into effect for nongroup members before benefits will be provided for care or treatment of any condition existing in any form on the effective date of the subscription agreement.

The best way to defeat compulsory health insurance is to render voluntary insurance more desirable. This the various medical-service plans of the country are successfully accomplishing.

"SING OUT SWEET LAND"

By action of the Council of the Massachusetts Medical Society taken at its annual meeting on May 23, the appointment of a co-ordinating committee to co-operate with the National Education

Campaign of the American Medical Association was confirmed. The committee, which has been functioning since April, is composed of the officers of the Society, the delegates to the American Medical Association, representatives from the committees on medical economics, legislation, public relations and the subcommittee on national legislation, the director of information and education, and the editor of the *Journal*. The chairman is Dr. Frank H. Lahey, former president of the American Medical Association.

The committee considers the time now appropriate to render an account of its activities as well as to offer its program for the future.

Of special importance has been the assembly that took place on May 1 at the Hotel Statler, to which each district society was invited to send ten per cent of its members. The attendance was estimated at six hundred and considerable enthusiasm for the campaign was evidenced.

A speaker's bureau has been established and some twenty physicians have given nearly three hundred talks before various lay groups. Editorial support has been elicited and numerous press and radio writers and commentators have supported the campaign to bring the Association's program before the public. Many lay groups have been active and a number of organizations have passed resolutions in support of the medical profession. Much literature has been distributed, and more is available at the Society headquarters.

Although the Government's campaign in favor of compulsory health insurance has been relatively inactive of late, the co-ordinating committee is planning its own future program. This is based largely on the activities of the district societies, most of which have not yet swung into satisfactory action, Franklin being a notable exception.

District co-ordinating committees must be set up where they are still lacking. Co-operation with the "Tell it to Twenty" division of the Massachusetts campaign must be strengthened, in order that a continuous flow of information to the list of twenty contacts made by each physician may make an informed group capable of substantial action and results at the proper time. Resolutions against compulsory national health insurance should be adopted by every district society and auxiliary. Local press and radio committees should be organized and contact made with local professional groups. Lay speakers must be enlisted, and above all the district woman's auxiliaries must be utilized in the campaign.

If socialized medicine is to form the wedge for a socialized state, it shall not be for lack of an informed and intelligent opposition.

DONORA SMOG

Of those few freedoms that remain to hunted man, the air he breathes has been considered as a fundamental right, common to all. Even the air, however, as the dweller in industrial areas well knows, may become as polluted by mechanical progress as are the water courses of the world's more advanced nations.

Uncontrolled (although largely controllable) smoke has been one of the by-products of the fiercely burning fires of industry, increasingly being shown to constitute a hazard to health as well as an offense to the eyes and a stench in the nostrils.

Especially spectacular were the conditions that prevailed for a short period last fall over Donora, Pennsylvania. Here, apparently as the result of static atmospheric conditions combined with the proximity of the American Steel and Wire Company zinc plant, a so-called "smog" descended over the city and presumably precipitated the deaths of twenty susceptible persons.

As a result of this episode the Public Health Service of the Federal Security Agency conducted a test in April to determine, if possible, the cause of the disaster. During the test the plant gradually resumed full production with no evidence of unfavorable conditions resulting. The assumption is that an unusual atmospheric state was necessary to trap in the valley of the Monongahela River the effluvium of the plant.

The knowledge is reassuring that lethal conditions will only occasionally result from the chance association of industrial production and bad weather. It is disturbing to realize that progress in public health must be made across the deserts and over the pol-

luted streams and through the poisoned air that man is himself creating.

Perhaps out of the almost forgotten disaster at Donora will come something more tangible than the perpetuation of an accordion-pleated word.

MOUSE TOWER

THE story, recently released, of Columbia's mouse dairy is another reminder of the unique relations that exist between mice and men. Rats and mice, for better or for worse—but principally the latter—have exercised their influence over human affairs since rats and mice and men began.

Hamelin had its experience with rats and learned too late that it pays to pay the piper. In the tenth century a singularly unworthy ecclesiastic, Bishop Hatto, having oppressed the peasantry of his fief and becoming annoyed at their protestations, shut them all into a barn, which he burned. Their squeals he likened to the squealing of mice.

As famine spread over the land a plague of rodents appeared, to escape which Bishop Hatto fled to his well stocked tower on an island in the Rhine. The Rhine, as history has shown before and since, proved no barrier to a determined invader. The mice crossed it, stormed the castle, and devoured the squealing bishop, presumably in some upper chamber.

Columbia's mouse tower in the College of Physicians and Surgeons, twelve years old and sixteen stories high, differs in its conception from that of Bishop Hatto.

At a cost of about $10,000 a quart, two quarts have been obtained annually from several thousand mice, each of which has been milked regularly (by suction), producing an average of 1 cc. of milk per pregnancy.

The result of this costly dairy, however, the story of which is contained in a release from Columbia University, has been a long forward step in the study of cancer. Certain strains of mice are peculiarly susceptible to a cancer of the breast that closely resembles the human form. The cancer virus has been isolated in the milk of these high-cancer-strain mice. This milk, when introduced into the systems of other mice, male or female, of low-cancer or high-cancer strain, by ingestion or injection, gives rise to cancer in a high percentage of cases.

The destructive rodent has made another part payment on the debt it owes to humankind.

Dr. Thomas Hooker was prosecuted in Canada, recently, on complaint of the College of Physicians and Surgeons, for practising physic without license, and fined £10 and costs. He had better come into New England, where any body can practise medicine, whether they understand it or not.

Boston M. & S. J., *August 22,1849*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

ALLEN — Harold M. Allen, M.D., of Lawrence, died July 3. He was in his sixtieth year.

Dr. Allen received his degree from Tufts College Medical School in 1913. He was a fellow of the American Medical Association.

His widow, a son and a daughter survive.

CLARK — Thomas F. Clark, M.D., of Taunton, died July 24. He was in his eighty-second year.

Dr. Clark received his degree from Harvard Medical School in 1901. For twenty years prior to his retirement in 1939, he served as head of the tuberculosis clinic for the city of Taunton. He was a charter member of the Bethlehem Home Corporation and was its first physician. He was a fellow of the American Medical Association.

His sister, three nieces and a nephew survive.

MATHEWS — Robert F. Mathews, M.D., of Worcester, died July 17. He was in his sixty-ninth year.

Dr. Mathews received his degree from University of Pennsylvania School of Medicine in 1905. He was a member of the American Urological Association and a fellow of the American Medical Association.

His widow survives.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATHS

PERKINS — Frank B. Perkins, M.D., of Manchester, died on June 21. He was in his ninety-fourth year.

Dr. Perkins received his degree from Dartmouth Medical School in 1877. He was the oldest living member of the Society.

A son survives.

SWEENEY — Frederick C. Sweeney, M.D., of East Jaffrey, died on June 22. He was in his eightieth year.

Dr. Sweeney received his degree from University of Vermont College of Medicine in 1895. He was a fellow of the American Medical Association.

Three sons, two daughters and sixteen grandchildren survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

APPOINTMENT

James A. McComb, D.V.M., has been appointed acting director of the Division of Biologic Laboratories, Massachusetts Department of Public Health. Dr. McComb succeeds Dr. Geoffrey Edsall, who has accepted the position of professor of bacteriology at Boston University School of Medicine.

Dr. McComb, who has been with the Department for twenty-two years, entered the Division of Biologic Laboratories as assistant bacteriologist and a year later was appointed senior bacteriologist. He has served as assistant director of the Division since 1942.

A veteran of World War I, Dr. McComb served in the Army as a sergeant in the field artillery. He was a lieutenant in the Army Reserve Corps for nine years.

He is a member of the American Veterinary Medical Association and the American Public Health Association.

RECOMMENDED PRACTICES FOR THE CONTROL OF POLIOMYELITIS

In view of the current prevalence of poliomyelitis, the Department and the Committee on Public Health of the Massachusetts Medical Society have endorsed a list of practices for the control of the disease. These practices, which were formulated by the National Conference on Recommended Practices for the Control of Poliomyelitis, held in Ann Arbor, Michigan, June, 1949, and are sponsored by The National Foundation for Infantile Paralysis, Inc., are in substance as follows:

The Disease

Recognition of the Disease

Poliomyelitis is a highly prevalent infection of which only a small fraction of the cases is clinically identifiable. In its recognizable form it is an acute illness, usually febrile, with early varying symptomatology, but usually with headache and almost always a characteristic stiffness of the neck and spine that justifies an examination of the spinal fluid. In about half such cases a lower neuron paralysis develops in the first few days of illness, which shows a marked tendency for spontaneous improvement after it has reached its height. If the patient is first seen after the acute stage has passed, the diagnosis depends upon detection of a flaccid paralysis characteristically irregular in its involvement of muscle or muscle groups. Diagnosis in nonparalytic cases depends upon detection of a clinical picture compatible with the illness, plus the demonstration of a moderate increase in cells in the spinal fluid. A form of illness presumptively poliomyelitis (abortive) presenting only vague symptoms and without signs referable to the central nervous system is of frequent occurrence during epidemics.

Etiologic Agent

The poliomyelitis virus is the etiologic agent. Several immunologically distinct types have been identified.

Source of Infection

The pharyngeal and fecal discharges of infected persons, frequently those not suffering from a clinically recognized attack of the disease, constitute the source of infection.

Mode of Transmission

Close association with infected persons accounts for the great majority of cases. Outbreaks attributable to milk have been rare and limited. Although flies have been found to be contaminated with the virus, there has been no reliable evidence of spread by insects, water, food or sewage.

Incubation Period

Usually 7 to 14 days. (May be from 3 to 35 days.)

Period of Communicability

Apparently the period of greatest communicability is covered by the latter part of the incubation period and the first week of the acute illness.

Susceptibility and Immunity

Susceptibility to infection is general. Immunity is acquired by infection which may have been clinically inapparent. The duration of immunity is unknown, but second attacks are rare.

Prevalence

Infection is prevalent throughout the world. Paralytic cases have been apparently more frequent in the temperate zones. It occurs both sporadically and in epidemics at irregular intervals, with the highest incidence in summer and early fall. In the United States an annual incidence of 10 paralytic cases per 100,000 population is ordinary, but there is a wide variation in incidence from year to year and region to region. Children from 1 to 16 years of age are more frequently attacked than adults. In several countries, including the United States, older children and young adults constitute a higher proportion of reported cases than formerly. Even during epidemics the incidence of paralytic cases has rarely exceeded one per thousand population.

Methods of Control

(*a*) Preventive measures: none.

(*b*) Through the infected person, contacts and environment.

Recognition of the disease by clinical manifestations assisted by microscopic and chemical examination of the spinal fluid if lumbar puncture is performed, and reporting it. In reporting, paralysis or its absence should be specified. A clear separation between these two groups of cases as reported permits a closer comparison of incidence between localities and with past experience.

Isolation: for one week from date of onset, or duration of fever if longer.

Concurrent disinfections: nose and throat discharges and feces are infectious and should be disposed of as quickly and safely as possible. Articles soiled therewith should be promptly disinfected.

Terminal disinfection: none.

Quarantine: quarantine is of unproved value. Modified quarantine restricting the movement of intimate contacts for 7 to 14 days may be desirable in certain circumstances. (In Great Britain 21 days of exclusion from school of child contacts is required.)

Active immunization: there is none, and passive immunization is not recommended.

Investigation of source of infection: this consists of the search for and expert diagnosis of sick children to locate unrecognized and unreported cases of the disease.

(*c*) Epidemic measures

General notice to physicians of the prevalence or increase of incidence of the disease, description of usual characteristics of the onset and the necessity for diagnosis and medical care, particularly for bed rest of patients, and information to the public at large on similar matters.

Isolation in bed of all children with fever, pending diagnosis.

Education in such technic of bedside nursing as will prevent distribution of infectious discharges to others from patients isolated at home.

Protection of children so far as practicable against unnecessary contact with persons other than their usual associates.

Postponement of elective nose or throat operations or dental extractions.

Avoidance of excessive physical strain (for example, violent exercise) in children during an epidemic or in case of known exposure.

Avoidance of unnecessary travel and visiting, especially of children, during a high prevalence of the infection.

The Patient

Reporting

All obvious and suspect cases should be promptly reported. As soon as possible all these cases should be classified as paralytic or nonparalytic. Cases which are finally diagnosed as presumptive (abortive) poliomyelitis should not be included in the final tabulation of cases by the health officers. For the guidance of health officers and physicians the following is proposed:

Diagnostic criteria of paralytic or nonparalytic poliomyelitis should generally include three or more of the following:

History compatible with poliomyelitis
Fever
Stiff neck or stiff back or both
Ten to 500 cells per cc. of spinal fluid taken during the acute or early convalescent period of the disease.
Spinal-fluid protein elevated above normal limits
Demonstrable muscle weakness or paralysis

Cases that present only a history compatible with poliomyelitis, and fever, should be classified as presumptive (abortive) poliomyelitis.

Paralytic cases are defined as those in which definite weakness or paralysis has been detected and has persisted during at least two examinations with an interval of at least several hours. Results of an examination for paralysis of muscles of the extremities or trunk may be very unreliable during the period of muscle tenderness or "spasm."

Hospitalization

(*a*) Admission to general hospital

Patients with acute poliomyelitis, or presumed to have acute poliomyelitis, are admissible to a general hospital provided that appropriate isolation precautions are employed. No special isolation or "pest" facilities are necessary.

(*b*) Nursing care

Special-duty nurses should be employed with regard only to the medical condition of the patient, and to the number of patients they can properly handle.

(*c*) Isolation technic in hospitals

The isolation procedures used for the care of acute poliomyelitis patients are similar to technics used in the hospital care of other communicable diseases, namely:

Segregation of patients having the same disease, preferably in single rooms or small wards. Patients can be cared for in large wards.

Washing of linen in the hospital laundry. Ordinary precautions for handling articles from infected persons are sufficient.

Sterilization of eating utensils after use.

Availability of toilets or hoppers in each room, small ward or large ward.

Availability of hand-washing facilities in each room, small ward or large ward.

Use of gowns by physicians when examining a patient and by nurses when caring for a patient, particularly while bedpanning.

Disposal of excreta of patients by placing in toilet or hopper as soon after passage as possible. The bedpan should be washed out if the utensil is used for a single patient, but when used in wards bedpans should be sterilized each time the utensil is used. No special treatment of feces from poliomyelitis patients is necessary.

Hand washing with ordinary soap and water should be practiced following examination of patients and after bedpanning a patient.

When toilet or hopper is situated outside the room or ward, a single pan should be covered and the contents disposed of as above; multiple pans are best cared for by being placed on a cart and transferred to the disposal unit.

(*d*) Care at home

Patients may be cared for at home if home facilities and medically supervised care are adequate; or may be discharged to such home when there is no medical indication for further observation or treatment in the hospital.

Admission to or care in a hospital for isolation purposes only is not usually indicated.

(*e*) Care of suspect cases

It is recommended that suspect cases when admitted to a hospital should be segregated when possible from known cases until the diagnosis has been established or the patient is discharged as well.

(*f*) Importation of patients

In order that the best possible facilities may be used for the care of cases of poliomyelitis, patients may be sent from their own home communities to a hospital in another community. The available evidence indicates that such importation of patients into a hospital in a community where poliomyelitis is not prevalent does not effect the incidence of the disease in the hospital community.

(*g*) Transportation of patients

Transportation of patients from one health jurisdiction to another may be carried out under proper conditions, such as transportation in an ambulance or a private vehicle. A common carrier should not be used. Transfer should be carried out with the knowledge and the consent of the health officers in the jurisdiction to and from which the patient is being transferred.

No special treatment of ambulances after their use by poliomyelitis patients is necessary.

The Community

These recommendations were formulated with the emphasis on avoiding the possible effect of disturbing or altering unnecessarily the normal pattern of life in the community. Whatever is done to upset the usual routine of children in a household or adults in their occupations is likely to bring more trouble than good.

Schools

Public and private schools should not be closed during an outbreak of poliomyelitis, nor their opening delayed, except as noted below:

The closing of schools, or the delay of their opening, has not affected the course of outbreaks of poliomyelitis; moreover, such action has often resulted in panic on the part of the public. The decision to open school as usual should be announced well in advance jointly by the superintendent of schools and the health officer, in collaboration with the local medical society.

Early in the season the state departments of education and public health should issue a joint statement to which local authorities can refer for support. This statement should be issued in collaboration with the state medical society.

Exceptions

Schools to which children are transported in busses from widely separated areas may be delayed in opening, if such action will prevent other close contacts among children. If these schools are not opened such action is justifiable only when other close contact among these children is not permitted in such places as theaters, picnics, playgrounds, swimming beaches or Sunday schools.

Boarding schools (excluding colleges and universities) should delay opening sessions if an outbreak of poliomyelitis exists in the area where the school is located and if the children are thus prevented from coming into the area from regions where the disease is not prevalent.

Nursery schools may be continued or closed depending upon the particular circumstances. Parents, if both are employed, may prefer to send their children to a nursery school. Parents who have facilities at home to limit contacts of young children with other children should be encouraged to keep preschool children at home.

Camps

Summer camps should be opened as usual if there is no outbreak of poliomyelitis in the area in which the camp is located.

Children should not be admitted from areas where an outbreak exists.

Inasmuch as there is no evidence that retention of children in camps where poliomyelitis exists leads to increased hazard, and that dismissal from camps may lead to spread to other communities, it is further recommended that if a case of poliomyelitis occurs in a camp the following procedures be instituted:

Retention of all children and staff at the camp for 14 days after the last contact with the case or until the usual closing date of camp.

Modified and supervised activity to prevent excessive exercise and undue mixing in group activities.

Careful medical checkup on all children daily.

Isolation of all children with fever or any suspicious signs and symptoms.

Discontinuance of admission of new children to camps in which poliomyelitis cases have been recently diagnosed.

Day camps should follow the same recommendations as those above pertaining to schools.

Places of Recreation and Amusement

It is recommended that health officers do not take action to close or prevent the operation of places of recreation or amusement, such as fairs, circuses, theaters, swimming pools or beaches, provided these are properly operated. However, the attendance of children at such places should be discouraged.

Any theoretical advantage that might be gained by closing such facilities is offset by the undesirable results of disruption of community life.

LOCATION OF RESPIRATORS AND HOT PACK MACHINES IN MASSACHUSETTS*

City or Town	Location of Equipment	Respirators	Hot Pack Machines
	BARNSTABLE COUNTY		
Hyannis	Cape Cod Hospital	1	1
	BERKSHIRE COUNTY		
North Adams	North Adams Hospital	1	—
Pittsfield	House of Mercy Hospital	3	5
	BRISTOL COUNTY		
Attleboro	Sturdy Memorial Hospital	1	2
Fall River	Fall River General Hospital	1	3
	St. Anne's Hospital	1	—
	Truesdale Hospital	—	1
	Union Hospital	2	2
New Bedford	St. Luke's Hospital	1 adult 1 chest 1 infant	2
Taunton	Morton Hospital	1	—
	ESSEX COUNTY		
Beverly	Beverly Hospital	2	1
Danvers	Hunt Memorial Hospital	1	—
Haverhill	Hale Hospital	1	—
Lawrence	Lawrence General Hospital	2	1
Lynn	Lynn Hospital	2	1
Newburyport	Anna Jaques Hospital	1	1
Peabody	J. B. Thomas Hospital	1	1
Salem	Salem Hospital	3	1
	FRANKLIN COUNTY		
Greenfield	Greenfield Isolation Hospital	1	1
	HAMPDEN COUNTY		
Holyoke	Holyoke Hospital	1	2
Springfield	Health Department Hospital	2	1
	HAMPSHIRE COUNTY		
Northampton	Cooley-Dickinson Hospital	1 adult 1 infant	1 —
	MIDDLESEX COUNTY		
Cambridge	Cambridge City Hospital	1 adult 1 infant	—
Everett	Whidden Memorial Hospital	1	—
Framingham	Cushing General Hospital	1	—
	Framingham Community Hospital	1	2
	Framingham Union Hospital	1	—
Lowell	St. John's Hospital	—	—
Malden	Malden Hospital	1	3
Newton	Newton-Wellesley Hospital	—	1
	NORFOLK COUNTY		
Quincy	Quincy City Hospital	1 adult 1 infant	1
Wellesley	Wellesley Convalescent Home	1	2
	PLYMOUTH COUNTY		
Brockton	Brockton Hospital	1	—
Middleboro	Lakeville State Sanatorium	2	3
	SUFFOLK COUNTY		
Boston	Beth Israel Hospital	2	—
	Boston City Hospital	7	3
	Carney Hospital	1	—
	Children's Medical Center	3†	10
	Haynes Memorial Hospital	6	5
	Massachusetts General Hospital	6	3
	New England Baptist Hospital	1	—
	Peter Bent Brigham Hospital	3	1
	St. Elizabeth's Hospital	1	—
	Veterans Administration Hospital (West Roxbury)	1	—
Chelsea	Chelsea Memorial Hospital	1	—
	Chelsea Naval Hospital	1	—
Revere	Revere General Hospital	1	—
Winthrop	Winthrop Community Hospital	1	—
	WORCESTER COUNTY		
Fitchburg	Burbank Hospital	1	2
Gardner	Henry Heywood Memorial Hospital	1	—
Worcester	Belmont Hospital	1	—
	Memorial Hospital	1	—
	Worcester City Hospital	3	—

*List compiled jointly by the Massachusetts Department of Public Health and the National Foundation for Infantile Paralysis.

†Also, 4-patient respirator room.

When called by a physician desiring assistance in diagnosing poliomyelitis in the acute stage, the fees of the following consultants will be paid by the county chapters of the National Foundation for Infantile Paralysis.

CONSULTANTS FOR THE DIAGNOSIS OF ACUTE POLIOMYELITIS

BOSTON	
Dr. William Berenberg 300 Longwood Avenue	ASpinwall 7-9250
Dr. Louis Weinstein 296 Allston Street, Brighton	ASpinwall 7-5750
BEVERLY	
Dr. Allen M. Hill 1 Monument Square	Beverly 4310
GREENFIELD	
Dr. Merritt B. Low 31 Federal Street	Greenfield 6832 (office) " 6775 (home)
Dr. Alexander S. Nadas 78 Federal Street	Greenfield 6992 (office) " 7647 (home) If no answer 5441
HOLYOKE	
Dr. George D. Henderson 176 Chestnut Street	Holyoke 2-8577 (office) " 2-9466 (home) If no answer 9611
LAWRENCE	
Dr. A. Ash 281 Haverhill Street	Lawrence 2-9375 If no answer 2-5221
LYNN	
Dr. Maurice T. Briggs 7 Lynn Shore Drive	LYnn 3-0223
MEDFORD	
Dr. Wallace J. Nichols 116 Forest Street	MYstic 6-0842
MELROSE	
Dr. Ralph W. Daffinee 8 Porter Street	MElrose 4-4100
NEW BEDFORD	
Dr. Charles S. Lipsitt 337 Union Street	New Bedford 2-1442
Dr. George W. Starbuck 34 Arnold Street	New Bedford 2-6277

NORTHAMPTON

Dr. Claire C. Manwell 16 Center Street	Northampton 857W

PITTSFIELD

Dr. James E. Breslin 74 North Street	Pittsfield 2-3389
Dr. George P. Hunt 131 East Housatonic Street	Pittsfield 6820
Dr. Floyd R. Smith 18 Bank Row	Pittsfield 2-5353 If no answer 2-1551

QUINCY

Dr. Marion L. Slemons 195 Upland Road	GRanite 2-4940

SALEM

Dr. Robert T. Moulton 39 Warren Street	Salem 2904

SPRINGFIELD

Dr Norman A. Pokorny 23 Maple Street	Springfield 6-1721 If no answer 6-7241

WORCESTER

Dr. Jacob Brem 796 Pleasant Street	Worcester 2-4544
Dr. Robert D. Cox 48 Kenwood Avenue	Worcester 2-1735
Dr. Alfred S. O'Connor 390 Main Street	Worcester 3-6557

CORRESPONDENCE

ACADEMY OF GENERAL PRACTICE

To the Editor: On May 26 an editorial in the *Journal* extolled the virtues of the American Academy of General Practice and the institution of a Massachusetts Chapter.

To be eligible for membership in the Academy a candidate must be a graduate of an approved medical school and have other qualifications. Several of my confreres have reminded me that the Massachusetts Medical Society and the American Medical Association grant membership and fellowship to graduates of unapproved medical schools in this Commonwealth. It would seem, then, that an Academy has been established that is not open to every reputable doctor who is qualified for membership in the organizations that sponsor said Academy. If this is not talking out of both sides of our mouths, what is?

Those of us who take responsibilities in medical organization cannot help but react to this challenge of our organization to intellectual honesty. We have seen hospitals that use the authority of the American Medical Association for their internships flagrantly disregard rulings of this same American Medical Association that helps keep them in business. Is it any wonder that individual members do not trust their organization? Is it any wonder that a sizable percentage of our membership would just as soon trust the domination of social workers and politicians as they would us?

Of course Massachusetts has a little different situation but that is no reason why we do not revolt about the point taken in this communication. Sometime this line of reasoning could lead to a qualification as to when, where, and why we were born. Those who might be considered radical in feeling the thoughts expressed here are really tremendously conservative in that they want to protect upright and hard-working, competent fellow practitioners and I am sure we would suggest that in this fight for our lives and existence, the medical profession in its organization still has not acquired the broad and liberal viewpoint that should be one of its most valuable assets.

W. A. R. Chapin, M.D.

121 Chestnut Street
Springfield, Massachusetts

Dr. Chapin's letter was submitted to Dr. James G. Simmons, secretary of the Massachusetts Chapter of the American Academy of General Practice, who offers the following reply:

Dr. Chapin has raised a number of questions about the American Academy of General Practice that I believe I can answer to his satisfaction.

The American Academy of General Practice is an entirely independent organization; it is not a subsidiary of the American Medical Association, nor is it connected with any state medical society. It was founded by a group of general practitioners because it appeared that there was a need for such an organization to advance the interests of the family physicians, and give them greater opportunities for education, both undergraduate and postgraduate.

However, it has had the full co-operation of the American Medical Association from the beginning. Dr. Paul A. Davis of Akron, Ohio, a member of the House of Delegates and chairman of the Section on General Practice of the American Medical Association, was appointed as its official representative at the original founding meeting in June, 1947. He became the first president of the Academy.

The Board of Trustees of the American Medical Association continues to co-operate through a co-ordinating committee to which the American Medical Association appoints three members representing the Board of Trustees, the Council on Medical Service and the Council on Medical Education and Hospitals.

Whereas the by-laws of the American Academy of General Practice provide that a candidate shall be a graduate of an approved school, the same by-laws give the board of directors of each state chapter the right to make exceptions to this rule under special circumstances.

Acting under this provision most of the state chapters have taken into their organization a number of graduates of other schools on the basis of their individual qualifications, their standing in their communities and the recommendations of their fellow practitioners. It is believed that the Academy can thus best carry out its purpose of raising the quality of general medical practice throughout the country. We believe that graduates of all schools can be helped by the Academy and that they in turn can help the Academy to become a great force for good in the medical community.

If your correspondent would like any further information about the Academy the officers of the Massachusetts Chapter would be very happy to talk with him personally or correspond with him in further detail.

James G. Simmons, M.D., *Secretary*

30 Myrtle Avenue
Fitchburg, Massachusetts

THE MORAL ISSUE

To the Editor: Dr. Leo Alexander's account of German "killers in white" in the July 14 issue of the *Journal* warns that we in this country must be on guard against a policy of inadequate treatment of dependent sick persons, mistreatment forced on doctors by an economy-minded public. But we must keep in mind that cruel and unmerciful treatment can be meted out in the very name of mercy and of religion. The atrocities committed by German doctors were acute; ours are long lasting.

Doctors who are custodians of children with undeveloped or misformed brains deny these pitiful creatures the mercy of natural death from infection. They give prophylactic inoculations and the wonderful new germ-killing drugs, and thereby force on these helpless creatures an indefinite number of miserable years. Their drawn-out misery is shared by their parents and by the many patients who could be helped but cannot gain entrance to our hopelessly clogged institutions.

I speak only of the near brainless and mindless creatures beyond reach of any medical miracle, now or ever. Doctors in charge cannot exercise their natural feeling of humanity and mercy because of the pressure of unknowing popular sentiment—ignorance that doctors in general make no effort to lighten. "Religious" hands raised in protest against the infectious friends of the permanently defective are, many of them, stained with the cruelly tortured blood of the Inquisition. "Be ye merciful" is a broad and compelling command.

William G. Lennox, M.D.

Boston

To the Editor: One of the most pertinent articles appearing in the *Journal* in recent months was in the July 14 issue, by Dr. Leo Alexander, entitled "Medical Science Under Dictatorship."

One is prompted to gratitude and applause that in some quarters, at least, beyond our preoccupation with pathophysiology and health insurance, the essential values that identify a doctor have been recalled.

Dr. Alexander's careful analysis indicates what happens to the physician when he takes materialism from society and turns to view his patient. He soon embraces the attitude of "scientism" as his philosophy. The person who is the doctor's patient becomes an "organism." His tired sclerotic arteries, on which depend the perilous balance of a family livelihood, give him a number in a statistical series. Because the patient is a "case," the doctor feels no more responsibility beyond giving him a "controlled study," and the medical conscience is at peace if it sends him off with the "latest form of therapy." From this materialistic outlook on man, the level of morality of the practicing physician, such as it is, is likewise materialistic, and his code then becomes "usefulness to society," utilitarianism, and rank sentimentality.

The science of medicine is one thing. The profession of medicine is quite another. The business of a practicing physician is undeniably linked to the Christian virtue of Charity. This implies the truth of man created by God. Herein lies the inherent dignity of man. From where else comes the logic of the argument against the practice of euthanasia? The hydrocephalic or the mongol may not be apparently "useful to society," but he is "useful" to God, by virtue of being His creature. Unless doctors abandon their subtle omnipotency, and realize that the values that define their profession are Christian values, their art will be reduced to a technic. Where do doctors meet this "scientism"? At the beginning—for four full years in medical school. As a recent graduate, I can vouch for the difficulty of a medical student's viewing man as anything more than viscera, muscle groups and "integrated reflexes." The honest respect that he has for his instructor's learned outline of anatomy and physiology is easily shifted to an identification with his materialistic innuendoes and — the "organism." In all the wealth of his clinical teaching, where is he told of the practice of medicine and the values underlying it? Exhortations to "treat the patient as a whole" are not enough. He must gain an idea why the patient is worth treating at all. I urge you, therefore, to look again at the medical schools.

J. Jerrold Applegarth, M.D.
The Roosevelt Hospital
New York City

To the Editor: You are very much to be commended for publishing Dr. Leo Alexander's excellent article, "Medical Science under Dictatorship." It not only is well written and scholarly, but does the long neglected task of pointing out fallacies in our own attitude toward medical practice.

It is reassuring to know that there are still some physicians who care about the moral aspects of the patient-doctor relation. How easy it is for us to become callous to the individual in order to perfect some technic supposedly for "the common good"! I hope that many of your readers will take his message to heart and that his acute perceptions will receive wide dissemination.

I hope, too, that this will not be the last article dealing with what may be called the philosophy of medicine. In the light of eternal values, this is really more important than the technical advances we are so careful and so prompt in reporting.

Congratulations, again, to you and to Dr. Alexander.

James E. Bowes, M.D.
89-05 Hollis Court Blvd.
Queens Village 8, N. Y.

THE OTHER SIDE

To the Editor: Having in mind the declaration by the Minister of Health, Mr. Bevan, in the House of Commons May 5, 1949, that "We cannot, obviously, without the most careful consideration and legal safeguards, push needles into people whether they want to have them pushed in or not" we maintain in reply to your editorial of July 7 entitled "Strange Bedfellows" that we neither lose our perspective nor depart from our apparently laudable purpose when we maintain that the right of the individual to escape vaccination or other compulsory measures can be achieved without jeopardizing the common good.

The Bill of Rights is largely concerned with the protection of the rights of minority groups, and the effect of these safeguards that are thrown around minority groups serves to provide the greatest possible protection that could be provided to majority groups. Obviously, under a system of voluntary vaccination, the unvaccinated cannot possibly expose to disease those who have been vaccinated against the disease. Since there were only 59 casesof smallpox reported in the United States in 1948 and since vaccination is not generally required in the majority of the states, the prevalence or absence of smallpox is apparently more influenced by so-called "unknown factors" than it is by compulsory vaccination in any form.

We wish to thank you for stating the purpose of the Bureau correctly and for presenting an accurate summary of our Bulletin 429.

H. B. Anderson, *Secretary*
Citizens Medical Reference Bureau, Inc.
1860 Broadway
New York City

DEPRIVATION AND RESTORATION OF LICENSES

To the Editor: At the meeting of the Board of Registration in Medicine held June 16, it was voted to revoke the registration of Dr. Earl G. Hersey of Milton.

At the meeting of the Board of Registration in Medicine held July 12, it was voted to restore the registration of Dr. Glenn F. Muntz, 6 St. Charles Street, Boston.

George L. Schadt, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Skin Diseases: A manual for practitioners and students. By James Marshall, M.D., B.S., M.R.C.S., L.R.C.P., consulting dermatologist, Central Middlesex Hospital, and director of venereal diseases clinic, Royal Northern Hospital, London. 8°, cloth, 363 pp., with 8 color plates. London: Macmillan and Company, Ltd., 1948. $7.50.

In this new manual the common diseases are given extended treatment, but the whole field of dermatology is covered to some extent. Syphilis is included, as well as the nails, hair, sweat and sebaceous glands, and the mucous membrane. There is a short chapter on tumors of the skin. Recent advances in therapy have been included to bring the manual up to date. The text is well organized, and the volume well pubished. There is a good index.

Irregular Discharge: *The problem of hospitalization of the tuberculous.* Prepared by William B. Tollen, Ph.D., Research Division, Co-ordination Service, at the request of the Department of Medicine and Surgery, Veterans Administration. 8°, paper, 64 pp. Washington: Veterans Administration, 1948. 20c. VA pamphlet 10-27.

In this small pamphlet a comprehensive study is made of the tuberculous patients in veterans hospitals who "walked out" or were lost track of before their required hospitalization and treatment had been completed (technically known as "irregular discharges"). Over 50 per cent of the discharges from Veterans Administration hospitals of living tuberculous patients were irregular, and only 45.6 per cent were regular. The patients with irregular discharges were still injuriously affected by tuberculosis and required further hospitalization. The problem as visualized is basically a social one for the community at large.

Synopsis of Psychosomatic Diagnosis and Treatment. By Flanders Dunbar, M.D. With the assistance of Jacob Arlow, M.D., and others, and members of the staff of the departments of medicine and psychiatry, Columbia-Presbyterian Medical Center, New York City. 12°, cloth, 501 pp. St. Louis: C. V. Mosby Company, 1948. $6.50.

This manual is written primarily for the general practitioner, and is intended to be a guide to the newer methods of diagnosis and treatment. An attempt has been made to follow Osler's outline, with the addition of new material to the sections on differential diagnosis and treatment. The text is well arranged, and the various chapters are written by specialists in their fields. There is a long bibliography and an extensive index. The volume is well published and should prove useful as a ready reference source.

Primary Anatomy. By H. A. Cates, M.B., professor of anatomy, University of Toronto. 8°, cloth, 478 pp., with 392 illustrations. Baltimore: Williams and Wilkins Company, 1948. $6.00.

This new treatise on anatomy is written for nonmedical students, including nurses, physiotherapists, occupational therapists, physical educationists and other interested persons. The treatment is by systems of the body, rather than by regions, because this method is easier for the beginner. The illustrations are schematic drawings prepared especially for these groups of students. The material is well arranged, and the book well published. The type is particularly good. There is an extensive index. The volume should prove valuable to nonmedical persons.

Emergencies in Medical Practice. Edited by C. Allan Birch, M.D., F.R.C.P., physician, Chase Farm Hospital, Enfield. 8°, cloth, 468 pp., with 113 illustrations. Baltimore: Williams and Wilkins Company, 1948. $7.00.

This composite work is written by nineteen specialists who have contributed articles in their special fields. The material is confined solely to emergencies of a medical character. The whole field of medicine is covered, and there are special chapters on emergencies in industrial medicine, at sea and in the air, and on medicolegal and other nonclinical emergencies. There is a good index. The volume is well published, but the use of a heavy filled paper is not justified by the two essential color plates. These could have been tipped into a lighter volume. The text was printed in Great Britain.

Hallmarks of Mankind. By Frederic W. Jones, D.Sc., M.B., B.S., F.R.S., F.R.C.S., Sir William Collins Professor of Human and Comparative Anatomy, Royal College of Surgeons of England. 8°, cloth, 86 pp., with 23 illustrations. Baltimore: Williams and Wilkins Company, 1948. $2.50.

This small volume contains the subject matter of two lectures delivered by the author in 1947. It expresses his theories of the evolution of man, which he has held for over thirty years. His two main contentions are that man, "considered solely from the point of view of structure, is an extremely primitive type" and that "more primitive in basal structure than the living monkeys and apes, man has his own remarkable structural specializations that distinguish him from all other mammals and appear to be his ancient hallmarks." The text is interspersed with pertinent illustrations. The publishing is excellent. The printing was done in Great Britain. The book is a necessary source of information to all persons interested in the subject of evolution.

The Surgery of the Stomach and Duodenum. By T. H. Somervell, M.A., M.B., B.Ch. (Cantab.), F.R.C.S. (Eng.), surgeon-in-charge, London Mission Hospital, Neyyoor, S. India, and examiner in surgery to the University of Madras. 8°, cloth, 546 pp., with 231 illustrations. Baltimore: Williams and Wilkins Company, 1948. $11.00.

The author of this special work on surgery had an extensive experience in India, where gastric and duodenal diseases are very prevalent. He believes that ligature of the gastric vessels and even vagotomy are preferable to gastrectomy for the average surgeon. His work is based on the literature of the subject, as well as his vast experience. Likewise, Dr. Somervell is impressed with the future of the transthoracic operation for surgery of the upper abdomen and especially the transdiaphragmatic method of Dr. Gardham, of London. These operations are described in detail in the chapter on esophagogastric conditions. The text is well organized. The preliminary chapters are devoted to embryology, anatomy, physiology, pain, diagnosis and operative methods in general. The following chapters deal with the various diseases and conditions of the stomach and duodenum. There is a special chapter on the gallbladder and pancreas in relation to gastroduodenal surgery. Short lists of selected references are appended to the various chapters, and a bibliographic index lists the authors of the references in alphabetical order. There is also a good index of subjects. The illustrations were mostly drawn by the author. The text was printed in Great Britain, and the type and printing are excellent. The book should be in all medical libraries and available to all surgeons interested in gastric and abdominal surgery.

Medical Manual. By William R. Feasby, M.D., medical assistant to the superintendent, The Toronto Western Hospital, and lecturer in physiology, University of Toronto. 16°, cloth, 162 pp. Toronto: University of Toronto Press, 1948. $2.25.

This small manual is intended primarily for senior students, interns and nurses. The text is intentionally brief, but an effort has been made to include the information needed for everyday use. The greater part of the text is devoted to materia medica, diet and clinical methods. There is a special chapter on legal considerations. There is a list of common diagnoses and a good index. The manual compares favorably with similar publications.

Physicians' Federal Income Tax Guide: For the preparation of 1948 returns and 1949 estimates. By Hugh J. Campbell and James B. Liberman. 1948-49 edition. 4°, paper, 96 pp. Great Neck, New York: Doniger and Raughley, Incorporated, $2.50.

This valuable manual should be owned by every physician. It explains in detail how to make out tax returns and estimates. The tables of professional deductions, nontaxable receipts and nonprofessional deductions are especially valuable. The pamphlet is well published.

Allergy to Cottonseed and Other Oilseeds and Their Edible Derivatives: Excerpts from testimony before the administrator, Federal Security Agency. In the matter of fixing and establishing definitions and standards of identity for mayonnaise, French dressing, and related salad dressings (docket FDC-51). Public hearing held at Washington, D. C., November 18, 1947 and January 6 to 8, 1948. 8°, cloth, 275 pp. Memphis, Tennessee: National Cottonseed Products Association, Incorporated, 1948. Free.

This volume contains the testimony of 6 expert witnesses on allergy to cottonseed oil and other oilseed products, and of 2 other experts concerning relevant factors of vegetable-oil technology. The testimony was given at public hearings held before the Federal Security Administrator on November 18, 1947, and January 6-8, 1948, in the matter of fixing and establishing definitions and standards of identity for mayonnaise, French dressing and related salad dressing. The evidence presented had to do with allergy to edible oils. The edition was limited to 300 copies and presented to all medical schools in the United States and to selected medical and scientific libraries with the intention of making the volume available to all interested persons. It is not for sale.

The British Encyclopaedia of Medical Practice, Including Medicine, Surgery, Obstetrics, Gynaecology, and Other Special Subjects. (Medical Progress 1948.) Editor-in-chief, Rt. Hon. Lord Horder, G.C.V.O., M.D., B.Sc., F.R.C.P., physician to the King, and consulting physician to St. Bartholomew's Hospital. 8°, cloth, 539 pp., with 5 illustrations. London: Butterworth and Co. (Publishers), Ltd., 1948.

This volume is the latest of a long series intended to portray the advances in medicine for the year 1948. It is issued to supplement the encyclopedia, and the series brings this large work up to date.

Clinical Urology: Essentials of diagnosis and treatment. By Lowrain E. McCrea, M.D., F.I.C.S., clinical professor of urology, Temple University School of Medicine, and attending urologist, Philadelphia General Hospital. Second edition. 8°, cloth, 503 pp., with 263 illustrations. Philadelphia: F. A. Davis Company, 1948. $6.50.

The first edition of this book was published in 1946, and the demand for a new edition so soon is evidence of its soundness and popularity. The text, which has been brought up to date and in a large part rewritten, is based solely on the experience, practice and opinions of Dr. McCrea. The volume is well published. The type is excellent, making for easy reading. There is an extensive index. The use of a coated paper makes the volume rather heavy for its size. The book should be in all medical libraries and should prove useful to all physicians interested in urology.

Acta Radiologica. Supplementum 65. *Intussusception in Children: Diagnosis and therapy with barium enema.* By Hans Hellner. 4°, paper, 120 pp., with 50 illustrations and 6 tables. Lund, Sweden: Hakan Ohlssons Boktryckeri, 1948. Swed. Crowns 15:—

Supplementum 68. *Carcinoma of the Tongue: A clinical study of 277 cases treated at Radiumhemmet, 1931-1942.* By Folke Jacobsson. 4°, paper, 190 pp., with 24 illustrations. Stockholm: Esselte Aktiebolag, 1948. Swed. Crowns 20:—

Supplementum 69. *A Pneumographic Study of the Temporal Horn. With special reference to tumours in the temporal region.* By Erik Lindgren. 4°, paper, 151 pp., with 239 illustrations. Stockholm: P. A. Norstedt and Sons, 1948. Swed. Crowns 25:—

Supplementum 70. *Studies on Back-flow in Excretion Urography.* By Olle Olsson. 4°, paper, 80 pp., with 18 illustrations. Lund: Hakan Ohlssons Boktryckeri, 1948. Swed. Crowns 20:—

Supplementum 71. *On the Transmission Through Skin of Visible and Ultraviolet Radiation.* By K. G. Hansen. 4°, paper, 106 pp., with 84 illustrations. Copenhagen, Denmark: Arnold Busck, 1948. Swed. Crowns 8:—

These supplements are all written in English and present the latest information on the subjects under consideration.

Language and Language Disturbances: Aphasic symptom complexes and their significance for medicine and theory of language. By Kurt Goldstein, M.D. 8°, cloth, 374 pp. New York: Grune and Stratton, 1948. $8.75.

This monograph on aphasia is divided into two main parts: the origin of aphasic symptoms; and case reports, pathologic anatomy and treatment. The discussion of treatment is limited to twenty pages. The literature of the subject is referred to throughout the text. The material is well organized and well presented. The book is well published and should be in the reference collections of all medical libraries and available to all neurologists. There is a bibliography of 332 items, as well as indexes of authors and subjects.

The Shame of the States. By Albert Deutsch. 8°, cloth, 188 pp., with illustrations. New York: Harcourt, Brace and Company, 1948. $3.00.

In this small volume Mr. Deutsch presents a camera-documented story of conditions in the public mental hospitals in the United States. During a period of eighteen months the author visited thirty state hospitals from coast to coast, and found shocking conditions in many. On some of the visits the author was accompanied by news photographers, and some of the pictures taken are reproduced in the volume. In two chapters the United States Army's Mason General Hospital, at Brentwood, New York, and the Brooklyn State Hospital are described as two of the better hospitals, despite the overcrowding at Brooklyn. Mr. Deutsch conferred with many experts, who could not point to any hospital as being the best in the land. All had their deficiencies, but, according to the author, "the fact is that not a single state mental hospital in the whole country meets all the minimum standards of care and treatment, established twenty years ago by the American Psychiatric Association." The concluding chapters have to do with the efforts to remedy the existing deplorable conditions.

The Case Against Socialized Medicine: A constructive analysis of the attempt to collectivize American medicine. By Lawrence Sullivan. 12°, cloth, 53 pp. Washington: The Statesman Press, 1948. $1.50.

Mr. Sullivan, in this small book, presents in short chapters a historical account of socialized medicine. The story is based principally on the sworn testimony of witnesses appearing before committees of the House and Senate.

NOTICES

ANNOUNCEMENTS

Dr. Salvador Jacobs announces the opening of offices at 66 Rogers Avenue, Lynn, and 416 Marlborough Street, Boston, for the practice of neurology and general psychiatry.

Dr. Frederick Rosenheim, formerly associated with the Judge Baker Guidance Center, announces the opening of an office at 122 Commonwealth Avenue, Boston, on September 6.

Dr. Nathaniel M. Stone, of 371 Commonwealth Avenue, Boston, will continue the x-ray practice of his former associate, Dr. John W. Meachen, at 332 Pleasant Street, Malden. Offices will be open at both addresses.

Dr. George J. Warren announces the opening of an office at 55 Broad Street, Lynn, for the practice of urology.

MASSACHUSETTS STATE SOCIETY OF EXAMINING PHYSICIANS

A meeting of the Massachusetts State Society of Examining Physicians will be held on Wednesday, November 16, at 6:30 p.m., at the Harvard Club in Boston. Following the dinner, Dr. Fred Jostes of St. Louis, Missouri, will present a paper on rehabilitation.

All physicians are cordially invited to attend.

TRAINING IN PSYCHIATRY

The United States Public Health Service under the National Mental Health Act has approved a grant for a trainee in psychiatry at the Walter E. Fernald State School situated 8 miles from Boston. The stipend is level 5, or $3000 per year. However, candidates at lower levels may be considered and the amount of the stipend adjusted to the level of the candidate's training. Training will be offered in mental deficiency, child psychiatry, and related psychiatric and neurological problems through supervised experience in the out-patient, in-patient, research laboratory, psychological, educational and social-service departments, as well as participation in staff meetings, seminars in basic psychiatry and neurology and in child psychiatry.

Applications including the candidate's qualifications or requests for further information should be forwarded to Dr. Malcolm J. Farrell, Superintendent, Walter E. Fernald State School, Waverley 78, Massachusetts.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 6–10. American Congress of Physical Medicine. Page iii, issue of March 24.

SEPTEMBER 8. Care of the Terminal Stage of Cancer. Dr. John W. Spellman. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

SEPTEMBER 28. New England Pediatric Society. Page 136, issue of July 21.

SEPTEMBER 28–30. Mississippi Valley Medical Society. Page xi, issue of July 14.

OCTOBER 3–MAY 19. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.

OCTOBER 11–15. American Society of Clinical Pathologists. Drake Hotel, Chicago.

(*Notices concluded on page xiii*)